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A PROOF OF THE REGULATORY INFLUENCE OF COD LIVER OIL ON CALCIUM AND PHOSPHORUS METABOLISM *

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The demonstration of the preventive and curative action of radiant energy and of the organic factor contained in cod liver oil in rickets has made studies of the action of these therapeutic agents of fundamental importance. At the present time, investigations indicate that the salts chiefly concerned in the disturbance in mineral metabolism which constitutes rickets are those of calcium and phosphorus. The experiments reported in this paper, begun in January, 1922, were planned to demonstrate whether or not cod liver oil exerts a regulatory influence on the calcium and phosphorus metabolism of rats.

Before describing the experiments, it seems advisable to point out certain facts recently discovered concerning the calcium and inorganic phosphorus content of the blood.

The concentration of calcium in the blood serum is apparently never above a value believed in normal children to be between 10.0 and 11.0 mg. per hundred cubic centimeters of serum, and in adults between 9.0 and 10.5 mg. per hundred cubic centimeters.[1] Kramer, Tisdall and Howland [2] state that the figures for the calcium concentration "are remarkably constant not only for the same animal but for animals of different species." The administration of certain calcium salts by mouth to animals on ordinary diets has not resulted in an increase of calcium in the serum, and the hypodermic and intravenous administra-

* Received for publication, June 12, 1923.
* Aided by a grant from the Loomis Fund.
* From the Department of Pediatrics, Yale University School of Medicine.

1. Kramer, Benjamin; Tisdall, F. F., and Howland, John: Clinical Significance of Calcium Concentration in Serum of Children and Possible Errors in the Determination, Am. J. Dis. Child. **22**:560-564 (Dec.) 1921. Halverson, J. O.; Mohler, H. K., and Bergeim, O.: J. Biol. Chem. **32**:171 (Nov.) 1917.

2. Kramer, Tisdall and Howland: Footnote 1, first refernce.

tion has produced only a temporarily rise.[3] If, however, the calcium concentration in the serum is low, it may be raised by the administration of certain calcium salts. A low blood serum calcium is constantly found in infantile tetany,[4] and frequently in rickets without manifest tetany [5] and in certain cases of nephritis.[1] It is not known to what extent calcium in the blood is ionized.

The inorganic phosphorus of the blood serum in normal children, Howland and Kramer report, averages 5.4 mg. per hundred cubic centimeters of serum, with a minimum of 4.0 mg. and a maximum of 7.1 mg.[6] The inorganic phosphorus is increased directly after the ingestion of food.[7] It varies with the phosphate content of the diet and is possibly influenced by many other dietary factors.[8] Meigs, Blatherwick and Cary [9] summarize their work on the inorganic phosphorus of the plasma of cows thus: "The concentration of phosphatide and of inorganic phosphate in the plasma are highly variable. Both can be made to vary by changing the amount of phosphorus supplied with the rations, though the variations induced in this manner show themselves most markedly in the inorganic phosphate." The inorganic phosphorus is higher, according to Howland and Kramer,[10] in breast-fed children (average, 6.1 mg.) than in artificially fed children (average, 5.1 mg.). In rickets, the inorganic phosphorus in the serum is usually low;[11] and in certain cases of nephritis, high.[12] Certain

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3. Clark, G. W.: J. Biol. Chem. **43**:89 (Aug.) 1920. Dennis, W., and Minot, A. S.: J. Biol. Chem. **41**:357 (March) 1920. Heubner and Rona: Biochem. Ztschr. **93**:187, 1919. Brown, Alan; MacLachlan, Ida F, and Simpson, Roy: Effect of Intravenous Injection of Calcium in Tetany and the Influence of Cod Liver Oil and Phosphorus in the Retention of Calcium in the Blood, Am. J. Dis. Child. **19**:413 (June) 1920.

4. Howland, John, and Marriott, W.: Quart. J. Med. **11**:289 (July) 1918. Kramer, Benjamin; Tisdall, F. F., and Howland, John: Infantile Tetany, Am. J. Dis. Child. **22**:431-437 (Nov.) 1921. György, P.: Jahrb. f. Kinderh. **49**:1, 1922.

5. György, P.: Footnote 4, third reference. Howland, John, and Kramer, Benjamin: Calcium and Phosphorus in Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105-119 (Aug.) 1921. Iversen, P., and Lenstrup, E.: Forhandlingerne ved første Nordiske Kongres for Paediatri, 1920 (cited by Howland and Kramer). Findlay, L.; Paton, D. N., and Sharpe, J. S.: Quart. J. Med. **14**:352 (July) 1921.

6. Howland and Kramer (Bull. Johns Hopkins Hosp. **33**:313 [Sept.] 1922) state that the normal value of the inorganic phosphorus in the blood serum of rats is between 7.0 and 8.5 mg. See also: Howland and Kramer: Footnote 5, second reference.

7. Greenwald, I., cited in a review: The Biochemistry of the Blood in Relation to Its Calcium and Phosphate Content, Med. Sc. **6**:470-482, 1922.

8. Meigs, E. B.; Blatherwick, N. R., and Cary, C. A.: J. Biol. Chem. **37**:1 (Jan.) 1919. Greenwald, I.: J. Biol. Chem. **21**:29, 1915.

9. Meigs, Blatherwick and Cary: Footnote 8, first reference.

10. Howland and Kramer: Footnote 5, second reference.

11. Footnote 5. Hess, A. F., and Unger, L. J.: Tr. Am. Pediat. Soc. **34**:208, 1922.

12. Greenwald: Footnote 8, second reference. Marriott, W. McK., and Howland, John: Phosphate Retention, Arch. Int. Med. **18**:708 (Nov.) 1916.

pathologic conditions, namely, granulating wounds [13] and healing fractures,[14] are accompanied by an increase in the inorganic blood phosphorus. In adults, the inorganic phosphorus is lower than in children.[10] The concentration of the inorganic phosphorus in the blood serum, therefore, is subject to wide variation, and a "normal" inorganic phosphorus level, as such, has been established only within considerable latitude. It seems best to speak of the "usual" value of the inorganic phosphorus rather than of the "normal" value.

EXPERIMENTAL DATA

For the study contemplated in this work, five experiments were performed. A basal [15] ration low in calcium, phosphorus and fat-soluble A was used. The variations desired in the calcium and inorganic phosphorus content of the rations to be used in the individual experiments were secured by adding to this basal diet different amounts of either calcium carbonate or disodium phosphate, or both. Five rations, therefore, were required, each differing from the others simply in its content of calcium and inorganic phosphorus.[16]

In each experiment, about sixteen rats, varying in age between 36 and 44 days, were used. The animals were kept on the ration chosen for a given experiment for thirty-five days. At the expiration of this period, one-half the animals were bled, and the calcium and inorganic phosphorus of the pooled blood serum was determined. The remaining rats in the group were kept on the same ration as before, but with the addition to it of 2 per cent. (by weight) of cod liver oil. At the expiration of ten days, these animals were bled and the calcium and inorganic phosphorus of their pooled blood serum were determined.

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13. Eddy, W. H., and Heft, H. L.: J. Biol. Chem. **55**:12, 1923.

14. Tisdall, F. F., and Harris, R. I.: Calcium and Phosphorus Metabolism in Patients with Fractures, **79**:884-887 (Sept. 9) 1922.

15. As shown in Table 1, the rations used in the individual experiments were practically identical in their content of sodium chlorid, ground whole wheat, corn, gelatin and gluten flour. These constituents constituted the basal ration.

16. The five rations as prepared were prescribed by Prof. E. V. McCollum, who characterized them (in a personal communication to the authors) as regards their calcium and phosphorus content, as follows: I, Low calcium-low phosphorus; II, Low calcium-moderate phosphorus; III, Low calcium-high phosphorus; IV, Optimum calcium-optimum phosphorus, and V, High calcium-low phosphorus. The calcium and inorganic phosphorus content of the diet which is optimum to ensure to the rat normal growth and reproduction is not accurately established; indeed, the problem is an exceedingly complex one, and probably a number of other factors beside actual quantities are of equal importance. So far as amounts are concerned, McCollum regards 0.60 and 0.45 per cent. for calcium and inorganic phosphorus, respectively, as amounts probably near those requisite. The ration used in Experiment IV closely fulfils these stipulations.

The animals were kept in roomlight in metal cages, which were suspended in racks so that there was opportunity for most of the excreta to drop beyond reach. No nesting material was provided.

The chemical examinations were made in each instance on the pooled serum from all the rats in a given group. The animals were bled under ether anesthesia by cutting the jugular vein (one or both) and the carotid artery (one or both), and allowing the blood to drop into a funnel and from thence into a centrifuge tube. In a few instances, the animals were anesthetized and decapitated, and the bodies bled into a funnel. The inorganic phosphorus of the serum was determined colorimetrically as the phosphomolybdate, titrated against a

TABLE 1.—*Summary of Data Regarding Experimental Diets*

Experiment	Wheat, Gm.	Maize, Gm.	Gelatin, Gm.	Wheat Gluten, Gm.	Dextrin, Gm.	NaCl, Gm.	$CaCO_3$, Gm.	NaH_2PO_4 12 H_2O, Gm.	Ca per 100 Gm. Diet, Gm.	P per 100 Gm. Diet, Gm.	Weight-Ratio Ca : P
I	33.00	33.0	15.0	15.0	3.0	1.0	...	....	0.01	0.29	1:29
II	35.15	33.0	15.0	15.0	...	1.0	...	0.85	0.01	0.38	1:38
III	33.45	33.0	15.0	15.0	...	1.0	...	2.55	0.007	0.59	1:81
IV	33.00	33.0	15.0	15.0	...	1.0	1.5	1.68	0.66	0.47	1:0.7
V	33.00	33.0	15.0	15.0	...	1.0	8.0	....	1.42	0.26	1:0.18

TABLE 2.—*Summary of Data Regarding Experimental Animals*

Experiment	No. of Rats	Average Age, Days	Days on Diet Before Cod Liver Oil	Before Administration of Cod Liver Oil			After 2% Cod Liver Oil for 10 Days		
				No. of Rats Bled and Killed	Ca*	P*	No. of Rats Bled and Killed	Ca*	P*
I	18	40	35	10	5.0	6.0	8	8.8	5.8
II	15	44	35	8	5.6	7.9	7	9.1	6.6
III	13	43	33	7	4.2	11.1	6	8.6	10.8
IV	20	43	35	10	7.6	6.6	10	9.0	5.5
V	14	36	35	8	10.1	1.3	6	10.7	6.0

* Ca and P determinations were made on the serum of pooled blood and are expressed in milligrams per hundred cubic centimeters of serum.

known standard. The general quantitative relations were those described by Briggs.[17] The calcium of the serum was precipitated directly as the oxalate (as suggested by Kramer and Tisdall [18]) and titrated against potassium permanganate.

In Tables 1 and 2 are summarized the data from the experiments. These data are schematically shown in the accompanying chart. In Table 1 are given the constituents and calcium-inorganic phosphorus ratios of the diets used in the individual experiments. In Table 2 may be found the details of each experiment as regards the age and number of animals; the calcium and inorganic phosphorus concentration of the

17. Briggs, A. P.: J. Biol. Chem. **53**:13 (July) 1922.

18. Kramer, Benjamin, and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921.

blood serum of some of the animals (number of animals given) after thirty-five days on the diet, and then in the blood serum of the remainder (number of animals given) after ten additional days on the diet with 2 per cent. cod liver oil added.

The following summaries of the individual experiments bring out the striking influence of cod liver oil on the concentration in the blood serum of the calcium and inorganic phosphorus. Attention will also be called to certain other interesting data.

Experiment I. The ration used in this experiment contained only a trace of calcium and 0.29 per cent. of inorganic phosphorus—a diet deficient, therefore, in both calcium and inorganic phosphorus, particularly the former. This deficiency is reflected in the blood as shown in the analyses of the serum of the ten rats killed at the expiration of thirty-five days. The inorganic phosphorus was slightly lower than the "usual" value, and the calcium was reduced to 50 per cent. of the accepted normal amount. At necropsy the animals showed rickets. When the blood of the remaining animals, which had received cod liver oil for ten days, was examined, it was found that the inorganic phosphorus was unchanged and the calcium had increased 76 per cent.—to 8.8 mg., almost the normal value.

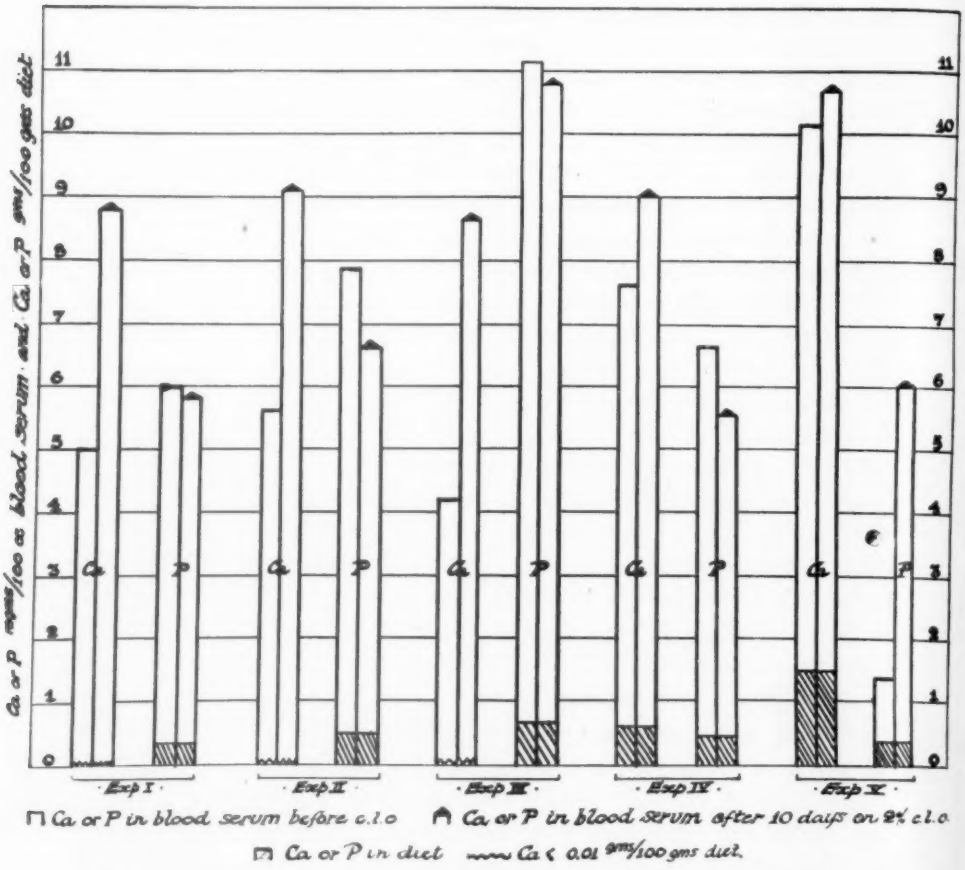
Experiment II. In this experiment also there was only a trace of calcium in the diet, but the inorganic phosphorus (0.38 per cent.) was nearer the "optimum" than in the ration used in Experiment I. The blood serum of the animals killed after thirty-five days showed a calcium concentration (5.6 mg.) which was almost the same as that found in the blood of the corresponding group in the preceding experiment. The inorganic phosphorus (7.9 mg.) was higher. Postmortem examinations revealed mild rickets. The influence of the administration of cod liver oil was the same as in Experiment I; i. e., there was no significant change in the inorganic phosphorus, and the calcium had increased 62 per cent.—to 9.1 mg., the normal value.

Experiment III. The ration used contained only a trace of calcium, but a great excess of inorganic phosphorus (0.6 per cent.), an amount probably considerably above the optimum. The results of this dietary as reflected in the blood serum of the animals at the end of thirty-five days is most striking, the calcium being low (4.2 mg.)—about 42 per cent. of the normal—and the inorganic phosphorus 11.1 mg., a value well above the usual.[19] Postmortem examination of these animals revealed marked rickets; the so-called low calcium rickets. After ten

19. There is, therefore, in these data, an excellent demonstration of the fact that the feeding of excessive amounts of the salts of phosphorus will force the level of the inorganic phosphorus in the blood serum beyond the value considered normal by Howland and Kramer (Bull. Johns Hopkins Hosp. **33**:313 [Sept.] 1922).

days of cod liver oil therapy, the inorganic phosphorus was unchanged and the calcium had increased about 100 per cent.—to 8.6 mg., almost the normal value.

Experiment IV. Here the ration is probably about optimum in its content of calcium (0.66 per cent.) and inorganic phosphorus (0.47 per cent.). The calcium and inorganic phosphorus of the blood after



Calcium and phosphorus levels before and after ingestion of cod liver oil.

thirty-five days was somewhat lower than the "usual" values. The addition of cod liver oil produced no striking change in the inorganic phosphorus or the calcium. At necropsy, the animals showed bones which did not differ greatly from the normal.

Experiment V. The diet used in this experiment regularly produces marked rickets of the so-called low phosphorus type. The ration contained an excess of calcium (1.42 per cent.) and a moiety of inorganic phosphorus (0.26 per cent.). The effect of this high calcium-

phosphorus ratio on the blood serum after thirty-five days was shown in a high calcium concentration (10.1 mg.) and in an extremely low inorganic phosphorus (1.3 mg.). At necropsy, these animals showed the classic signs of rickets. When the blood serum of the remaining animals, which had received cod liver oil for ten days, was examined, it was found that the inorganic phosphorus had increased over 360 per cent.—to 6.0 mg.—and the calcium was unchanged.

COMMENT

Data similar to those presented in this paper have already been furnished by Howland and Kramer [20] as a result of their calcium and inorganic phosphorus determinations on the groups of rats used by McCollum, Simmonds, Shipley and Park in experiments on rickets. The variations in the calcium-phosphorus ratios in the diets used and the corresponding changes in the blood serum were not so great as in our experiments.

The experiments [21] presented here show that when radiant energy and the organic factor contained in cod liver oil are deficient, certain disproportions in the calcium and phosphorus of the diet produce corresponding disproportions in the concentration of these elements in the blood serum. These findings are in accord with investigations already referred to in this paper. They are emphasized here simply because the demonstration is unusually clear cut.

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20. Kramer, Benjamin, and Howland, John: Bull. Johns Hopkins Hosp. **33**:313 (Sept.) 1922.

21. The experiments are not free from the possibility that they yield data technically correct but susceptible to incorrect interpretation and correlation. The relationship of the salt concentration in the blood serum to the ingestion of food may have been such as to give values, particularly as regards the inorganic phosphorus, which were neither "normal" nor "usual." While this criticism is valid, it is not pertinent to the subject of inquiry in this experiment; namely, the determination not of standards but of relations under the influence of specific dietary ingredients. In order to maintain, as nearly as possible, constant relations, the bleeding of the rats in each experimental group was always begun at the same hour of the day.

The slight variation in the initial ages of the rats in the several experimental groups, as well as the added ten-day period of life of those animals receiving cod liver oil, brings forward the question of the variations with age of the concentration of inorganic salts in the blood serum. It was impossible to get animals of identical age in the required number. A certain period on the diet plus cod liver oil had to be chosen. Clear-cut healing effects of cod liver oil on human rickets are demonstrable in the blood serum in about ten days, and that interval accordingly was chosen for these experiments. It has not been shown that variations with age *per se* occur in the concentration of salts in the blood serum of rats. Such variations, however, may take place. In any case, the changes which may occur with variations in age in the calcium and inorganic phosphorus in the blood serum of animals, either on diets considered normal or on those defective in their salt content, are probably slight compared with those here attributed to the influence of cod liver oil.

The experiments demonstrate in a striking manner the regulatory power of cod liver oil on the calcium and phosphorus metabolism of the organism. The changes in the concentration of the calcium and inorganic phosphorus of the blood serum which occurred under the influence of cod liver oil were striking in degree. No less striking was the constancy with which the concentrations moved toward those found in the blood of healthy rats on ordinary diets. It is an extraordinary fact that a substance containing neither calcium nor phosphorus, when administered to an animal whose blood is deficient in these elements, should have the power to cause the calcium or the phosphorus, as the case may be, to rise to, or nearly to, the level commonly regarded as normal and thereby to establish the normal equilibrium. Cod liver oil has this extraordinary power.

Cod liver oil not only acts as a regulator of the calcium and phosphorus metabolism, but also permits the organism to operate with greatly increased economy. In the presence of calcium or phosphorus starvation, cod liver oil enables the animal to get along as if the calcium or the phosphorus were supplied in sufficient or almost sufficient quantity in the diet. It is necessary to suppose that cod liver oil brings about maximal utilization of the minimal quantities of calcium or phosphorus in the diet. It greatly reduces waste of these elements and, therefore, must bring about maximal absorption from the alimentary tract. In human rickets, for example, the organism has lost its power to assimilate and to hold lime salts; if fed in large amounts, these salts are simply excreted. Cod liver oil (or radiant energy) furnishes something to the body which enables it to assimilate and hold lime salts. Obviously, cod liver oil makes the metabolic processes of the body, in respect to calcium and phosphorus, vastly more efficient. Its power to exert a regulatory influence on the calcium or phosphorus metabolism is perhaps to be regarded as an expression of an increased body efficiency.

What is the mode of operation of cod liver oil and by what means does it produce its extraordinary effects? On this problem of extreme interest no light can be shed at the present time. Certain it is that cod liver oil itself does not supply the deficient element. The existence of a latent period before the effect of cod liver oil becomes manifest makes it altogether likely that the effect of the oil is general and not limited to the alimentary tract. The almost exact similarity between the effects of cod liver oil and of radiant energy on the calcium and phosphorus metabolism of the body, and the existence of a similar latent period before the effects of radiant energy become manifest are additional strong evidence that the cod liver oil acts on the body as a whole rather than on the alimentary tract alone. Cod liver oil probably supplies something which is essential for optimal cellular function.

According to our conception, in the absence of the factor or factors contained in cod liver oil, and in the absence of radiant energy, the organism is laboring under a load, and the changes in the calcium and phosphorus metabolism resulting from the administration of cod liver oil are to be thought of as the result of the release from the load. The healing brought about by cod liver oil in rickets probably denotes in reality the manifestation of a restoration of normal function. Cod liver oil or radiant energy cannot be regarded in any sense as exerting a specific influence on calcium and phosphorus metabolism. The power to raise the calcium in the blood, when the calcium is low, or the phosphorus when that is low, is merely an isolated example of an effect which happens to be visible and measurable. Doubtless, cod liver oil and radiant energy will be found to have similar regulatory and efficiency producing effects in all conditions in which the organism is suffering as a result of a deficiency in the factor contained in cod liver oil or in radiant energy. When the human organism is deprived of the influence of radiant energy and of the factor or factors contained in cod liver oil, it loses its power to make successful adaptations to faulty environmental or dietetic conditions. What cod liver oil accomplishes in rickets is nothing more or less than the restoration to the organism of its power to make a successful adaptation to a faulty diet and a faulty environmental condition (roomlight). The evidence at hand does not indicate that cod liver oil or radiant energy causes the body to bring into action new or unusual processes, but rather that it restores to the organism power to utilize in the normal way and for the normal purpose those which were in operation all the time.

The similarity between the action of cod liver oil and that of radiant energy in rickets is so close that a connection must exist between them. So far as the calcium and phosphorus metabolism of the body are concerned, cod liver oil seems to be a substitute for radiant energy. It will be most interesting to see if, in the near future, a relation between cod liver oil and radiant energy will not be established of such nature that their effects will be explicable on a single basis.

THE HISTORY OF COD LIVER OIL AS A REMEDY*

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The revival of the use of cod liver oil in therapeutics and the newly awakened interest concerning its action have stimulated this inquiry into the history of its employment in medicine. The use of fish oils in medicine is mentioned by Hippocrates,[1] and Pliny[2] writes that the oil of the livers of the dolphin was used for chronic eruptions of the skin, not only as an external application, but also internally. No definite mention of the oil from the various species of *Gadus* is found in Greek and Roman literature (Bennett). Apparently, however, cod liver oil has been used by the fisherman along the coasts of northern Europe for many years. It is stated that, in the Island of Shetland and the north of Scotland generally, the liver of the cod has long been considered a special delicacy, and hence is given to invalids and people in poor health, particularly for "old pains,"[3] and that the fresh oil from the livers was used as butter and considered especially delicious. The use of cod liver oil by physicians was first recorded in England by Darbey at the Manchester Infirmary in 1789, who wrote:

> A woman who laboured under the most excruciating rheumatism, and was an outpatient of this infirmary, being advised to rub her joints with the oil, was induced to take it at the same time internally. A few weeks restored her to the use of her limbs, and she was cured. However, little attention was paid to this case, as it was supposed that the alteration of the weather, and the medicine she had before taken, had caused the cure. About a twelvemonth afterwards, her complaints returned with double violence, and the same remedy restored her to health again. Encouraged by this second recovery, Dr. Kay (1766), one of the physicians to the infirmary, prescribed it for other patients, in similar cases; and it answered his most sanguine expectations. Since then, it has been used by the other physicians with the greatest success.[4]

The popularity of cod liver oil for chronic rheumatism became so great at the Manchester Infirmary that "near a hogshead annually" was used there. In 1771, Percival entered it in the British Pharmacopaeia; later, in 1790, he wrote thus of its effect in chronic rheumatism:

> While I was one of the physicians to this charity [Manchester infirmary], I had the fullest evidence of the successful exhibition of cod liver oil, in various maladies, of the class above described, which had resisted other power-

* Received for publication, June 12, 1923.

* From the Department of Pediatrics, Yale University School of Medicine.

1. Fedotoff: De oleo Jecoris Aselli, Diss. Leipsic, 1842.
2. Pliny: Nat. Hist., Lib. **32**, p. 27.
3. Bennett: Treatise on the Oleo Jecoris Aselli, Edinburgh, 1848.
4. Percival's Essays, Ed. 4, 2:360, 1790.

ful modes of treatment. And I frequently compared its operation with that of gum guaiacum, by prescribing each, at the same time, to different patients in similar circumstances. These trials almost always terminated in favour of the oil; and the patients, who took guaiacum, by conferring with their fellow-sufferers, were sometimes so sensible of making a slower progress toward recovery, as to request a change of one remedy for the other.

The observations of Dr. Bardsley [5] (1807) concerning its employment at the Manchester Infirmary also are interesting.

From long and repeated experience, I am enabled to speak of it as a medicine of efficacious, but limited powers. In some instances, where every other means has proved unsuccessful, it has operated in a manner so decidedly beneficial, as to excite astonishment. But, on the other hand, it has frequently failed in some of the mild, and more common rheumatic affections. The circumstances under which I have found it most advantageous, when used both externally and internally, are the following: 1. In the chronic rheumatism of elderly persons, where the muscles and tendons have become rigid, and the joints nearly inflexible, in consequence of the disease having been brought on by excessive labour, hard fare, dampness, and cold. 2. In women whose constitutions have been worn out by repeated rheumatic attacks after parturition, and more especially in the decline of life. I have seen a few patients recover entirely by the exhibition of the oil; who, on their admission into the house, were unable either to preserve the body in an erect posture, or support its weight on the lower extremities.

It seems very probable that some of the cases of "rheumatism" in which the effects were "so beneficial as to excite astonishment" were osteomalacia.

Although undoubtedly cod liver oil continued to be a family remedy in different parts of the country, apparently it was little used by physicians during the next thirty years. At any rate, in the English medical literature of that period, no further mention of it has been found until its revival in 1841 by Bennett,[3] who had traveled in Germany and had observed its employment there.

In 1822, the Society of Science and Arts of Utrecht made the chemical and therapeutic properties of cod liver oil the subject of a prize essay.[6] Apparently, therefore, its use in scrofula and rickets was known to the Dutch medical profession at that time. Bennett states that, in Holland, it had obtained a wide reputation for the cure of rickets long before its remedial properties were acknowledged by medical men.

In the same year (1822), Schenck [7] published the first German article on cod liver oil as a therapeutic agent. This article deals with the details of a number of cases of rheumatism and gout which were greatly relieved or entirely cured by cod liver oil.

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5. Quoted from Bennett (Footnote 3), p. 72.
6. Hufeland's Journal **56**:128.
7. Schenck: J. d. pract. Heilk. **55**:31, Part 6.

Schütte,[8] in 1824, published the first definite case histories of rickets cured by cod liver oil, stating that he had used it for twenty-five years. The cases he cited were in children, from 3 to 5 years of age, and unable to walk, who were cured in from five to nine weeks. In each instance, the parents or relatives had prescribed the remedy. He definitely attributed to Percival the introduction of cod liver oil into medical literature.

In 1826, Schenck[9] reported its successful use in four cases of rickets. He wrote:

> I am able to recall that my venerated teacher Michaelis in Marburg recounted to us in his lectures in special therapy, under the chapter on chronic rheumatism, that he had during his stay in England at the hospital in Manchester seen cod liver oil used with striking success against chronic rheumatism.

From this time on, numerous German authors wrote on the subject, and cod liver oil became very generally used throughout Germany for rheumatism, gout and rickets, and hence for scrofula and tuberculosis.

Even before the middle of the century accounts of failure and of contaminations and substitutes for real cod liver oil appeared in the literature. So great was the demand that all sorts of substitutes were used. In one instance, a substitute was even flavored with decayed herring to give the characteristic offensive taste and smell.

The introduction of cod liver oil into France, which came a few years later than in Germany, is described by Trousseau:[10]

> The manner in which M. Bretonneau, of Tours, was induced to give the oil in this disease deserves notice. He had treated the rachitic child of a rich Dutch merchant with preparations of iodine and other means, for some time, without success. He was then told by the father that the elder children had previously suffered under the same malady, and had been cured by the cod liver oil, which, in Holland, was a popular remedy. Bretonneau gave the same substance to his young patient, and was much struck with the very rapid and successful result which followed. He commenced making researches with it on other patients, and it was only then that he learnt for the first time what had been written by the German authors on this subject. He has since given it extensively in rachitis, with the happiest results. This fact was communicated to the Societe de Medecine de Paris, in 1837, by M. Roche.

In 1836, de Villards[11] published the first article in France on its therapeutic value, but it was not until Trousseau, about the middle of the century, taught of its use and related the experiences of his celebrated colleague Bretonneau that it became generally known and recommended.

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8. Schütte: Arch. f. med. Erfahrung **79,** 1824.

9. Schenck: Hufeland's Journal **62,** 1826; J. der pract. Heilk., 1826, Part 3, p. 2.

10. Trousseau: Clinical Medicine, Philadelphia **2**:734, 1882.

11. De Villards: Schmidt's Jahrb. **5**:147.

In each country, the experience was the same: Cod liver oil was used by the fishing people and peasantry; then accidentally observed by some physician, tried by him, and so made known generally to the profession. At first, it was used in chronic rheumatism and gout; then, naturally enough, in other bone and joint diseases, notably rickets and osteomalacia (which was considered closely allied to gout); then in scrofula, because of its supposed identity with rickets, and finally in other forms of tuberculosis. It is interesting that its use in tuberculosis should have been by the way of rickets and gout.

It is interesting, too, that despite the fact that it was so effective in rickets and despite the fact that this efficacy had been observed and carefully recorded by reputable and well-known medical writers, it should have fallen into such widespread disuse. It is well recommended and reported as late as the middle of the nineteenth century; but late in that century and early in this one the textbooks of pharmacology all speak of cod liver oil as being useful in tuberculosis and rickets because, and only because, it is an easily digested and easily assimilated fat (Potter, 1902; Stevens, 1903; Penzoldt, 1904; Hare, 1907; Cushny, 1911 and 1915; Sollmann, 1917). At the same time appear numerous notes as to the detection, in samples then on the market, of adulteration or substitution of other oils, and also clinical reports both of success and of failure in its therapeutic use. Heubner, Salge, Baginsky, Biedert and Fischl found it of no use in rickets. Vierordt, Stöltzner and Finkelstein maintained a vigorous defense of it, although they emphasized the importance of combining it with phosphorus. From 1908 to 1912, Schabad published the much-discussed metabolism experiments, which indicated a specific effect in rickets not produced by other oils. He pointed out certain pitfalls in relation to latent period and dosage. In 1910, Rosenstern [12] wrote: "Cod liver oil is in the forefront of children's remedies. For long it has been struggling against the scepticism of exact science." He reported cures in cases of early rickets and tetany with cod liver oil alone, and considered the effect specific. Czerny,[13] in 1912, asserted most positviely that its only effect was due to its easily assimilated fat. No definite reports of its failure in actual use appeared in the literature in this country or in England. However, pharmacologists and chemists were convinced that its action was in no way specific, and certain noted pediatricians, whose influence was widespread, taught that it was of no particular value. In the 1901 edition of Rotch's [14] "Pediatrics," he says:

> The treatment of rachitis is essentially dietetic and hygienic. The infants should be kept in the open air as much as possible, and should live in rooms

12. Rosenstern: Berl. klin. Wchnschr. **47**:822, 1910.
13. Czerny: Therap. d. Gegenw. **80**:49, 1912.
14. Rotch, T. M.: Pediatrics, Philadelphia and London, 1901, p. 341.

accessible to sunlight. There does not seem to be any drug which produces specific effect upon the osseous changes which take place in rachitis. Phosphorus is considered by some observers to be a valuable adjunct in the general dietetic and hygienic treatment, but, according to our experience at the Children's Hospital, it has not proved to be of any special benefit.

He makes no mention of cod liver oil.

Still,[15] in his textbook, in 1912, notes the use of cod liver oil and gives the dosage, and adds:

There seems to be no specific virtue in cod liver oil, any other oil will do equally well, provided it can be taken without disturbing digestion or causing nausea by its taste. At one time we used, at the Children's Hospital, Great Ormond Street, olive oil and pilchard oil and cotton seed oil, made into as palatable an emulsion as possible, and these seemed to be as useful as cod liver oil, except that they were more apt to cause nausea or digestive disturbance.

Henoch, 1882;[16] Meiggs and Pepper, 1886;[17] Starr, 1894;[18] Holt, 1896;[19] Kerley, 1907,[20] and Fischer, 1907,[21] in their general textbooks, advised the use of cod liver oil, and many physicians were impressed with its obvious benefit in rickets and continued its use. Recently, well controlled experiments both in the rat and in the human infant have demonstrated beyond criticism the efficacy of cod liver oil in the cure and prevention of rickets, and attention may now be directed to the mechanism which brings about this effect.

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15. Still, G. F.: Common Diseases of Childhood, London, 1912, p. 103.
16. Henoch: Lectures on Diseases of Children, London, 1882, p. 335.
17. Meiggs and Pepper: Practical Treatise on Diseases of Children, Philadelphia, 1880, p. 705.
18. Starr: American Textbook of Diseases of Children, New York, 1894.
19. Holt, L. E.: Diseases of Infancy and Childhood, New York, 1896.
20. Kerley: Treatment of Diseases of Childhood, New York, 1907, p. 443.
21. Fischer: Diseases of Infancy and Childhood, Philadelphia, 1907, p. 353.

THE ANATOMIC BASIS FOR INTERPRETING ROENTGENOGRAMS IN RICKETS*

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For many years, clinicians have been familiar with certain of the features which characterize the roentgenograms of rachitic human bones; but a careful analysis of them has not been made, nor has the interpretation of the picture in the light of histologic alterations received any great attention. This investigation, which was begun at the suggestion of Dr. E. A. Park and carried on largely through his continued interest, was undertaken with a view to ascertaining the anatomic basis for the roentgen-ray changes in the skeleton in rickets.

METHOD

The bones selected for study were cleaned of surrounding tissues and cut into slices from one-eighth to one-quarter inch thick through the epiphyseodiaphyseal junction. Roentgenograms were obtained, and the slices were then used for the preparation of histologic sections. Some of the tissues were partially decalcified in Müller's fluid; but in many instances, it was found possible to cut sections without preliminary decalcification. The celloidin technic was used throughout. The sections were stained either with hematoxylin and eosin, by Mallory's method, or with hematoxylin and silver nitrate, as suggested by Von Kossa.

In studying the material obtained from thirty-five cases, comparisons were made between the histologic sections and the roentgenograms in order to ascertain the elements in the former responsible for the characteristic shadows of the latter. It was hoped that by this method some new facts would be found which would make possible an earlier clinical diagnosis.

ROENTGENOGRAMS IN RICKETS

The roentgenographic changes which occur in the bones of the extremities in the course of rickets will be considered first. The discussion will be limited to alterations of a more or less fundamental nature. One of the most constant findings when the roentgenogram of a bone during the active stage of rickets is examined is the general rarefaction. This varies in degree but is undoubtedly present to a cer-

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* From the Department of Pediatrics, The Johns Hopkins University and the Roentgen-Ray Department of The Johns Hopkins Hospital.

tain extent in every case, although it will be overlooked when of a mild degree on account of the lack of any standard for comparison. In other cases, the general osteoporosis may be most conspicuous, and the shafts of the bones may appear as nearly transparent shells, not much more dense than the surrounding tissues.

Little change is to be noted in the cartilage at the ends of the bones. In normal as in rachitic bone, the outline of the epiphyseal cartilage is generally invisible because its density is the same as that of the surrounding softer tissues. But, because of changes which make the shaft appear shorter, the cartilage will necessarily seem longer, or the distance between the shaft and epiphyseal center will seem greater; although, on close observation, it is at times apparent that, in the region where the added length seems to be, that is, between the true cartilage and the visible shaft, the density is slightly less than in the cartilage itself. The signficance of this area will be referred to later.

Probably the most definite signs are to be found at the ends of the shafts of the bones where they unite with their cartilages, more particularly in those locations where growth is proportionately rapid, the costochondral junctions of the middle ribs; the upper ends of the tibia and humerus, and the lower ends of the femur and radius. Clinically, we are all familiar with the enlarged epiphyses of rickets, and the rachitic rosary formed at the costochondral junctions. This enlargement is evident in roentgenograms. On account of accompanying rarefaction, its full extent often will not become visible until healing is moderately well advanced.

The changes at the ends of the shafts are more characteristic. In roentgenograms of normal bones, the line of termination of the shaft is quite sharp. It appears either as a single line of slightly greater intensity than the rest of the shaft; or, more frequently, in a sharply focused plate, the line will be double, this double line being the boundary of the surface in which the shaft terminates. In the rachitic bone, the sharp termination disappears, and the shaft fades away into the cartilage by a succession of less and less intense shadows. The transition may be very gradual, so that the shaft seems to be capped with a fringe an inch or more in width; or it may occur quickly, and at times abruptly. Sometimes, it may be observed that, at the base of this fringe, the shaft is crossed by a definite line of increased density, suggesting the termination of a normal shaft with a fringe sprouting from it. With the onset of healing, a definite line, at times seeming double because it is the boundary of a surface, appears on the epiphyseal side of this fringe, and will thus be separated from the shaft by a distinct hiatus. As healing progresses, the line thickens, and the hiatus gradually disappears.

Another alteration is frequently observed. The shaft is longer at its periphery than in the middle. In mild cases, there is only a small lip of bone at the edges, extending just beyond the line of termination of the middle portion of the shaft; in a more advanced state, the whole end of the bone appears concave. By the use of stereoscopic plates, it can be demonstrated that the actual deformity consists in a hollowing out or a cuplike depression of the ends of the bones. The cupping is much more striking when the termination of the shaft has been sharply outlined by the healing process.

In many cases, the cortex of the bone presents no characteristic changes. In others, especially when the disease has been of long duration, it is frequently observed that the cortical lamellae have lost their compact structure, and have become arranged in a much more loosely woven pattern. This appearance of lamination has not been generally appreciated, but seems to be as characteristic of rickets as any other.

Although, as a rule, the periosteum, in rachitic as in normal bone, is not visible, at times it may appear raised from the cortex and markedly thickened, resembling closely the roentgenogram in a syphilitic periostitis. It may not be possible to differentiate the two. It is to be observed, however, that the periosteal trabeculae produced by a rachitic hyperplasia at times tend to assume a stepladder appearance; that is, to lie at right angles to the long axis of the bone. A distinct hiatus is invariably observed, separating the periosteum from the cortex. The thickened periosteum is more frequently found on the concave side of the long axis of the bone than on the convex side. No such predilection is shown by syphilis.

The thickened periosteum is more commonly seen in the picture of rickets in its healing phase. A child who has active rickets may give no roentgenographic evidence that the periosteum is involved, and yet, a few weeks later, when healing is in progress, the plates will show plainly the effect of marked periosteal hyperplasia, so pronounced that it must have been present when the first picture was taken.

The changes observed in the epiphyseal centers of ossification, while similar to those in the shaft, are of particular interest. The degree of rarefaction is often pronounced; indeed, it may be so marked that the entire nucleus is rendered invisible or appears as a punched out hole in the center of the epiphyseal cartilage. In other cases, when the disease had set in before the time of the appearance of the nucleus of ossification, it may never have been visible by means of the roentgen ray. Epiphyseal centers which are visible during the active stage of the disease lose their normal sharp outline and, like the ends of the shaft, fade gradually into the cartilage. After the beginning of antirachitic therapy and the establishment of healing, a previously

invisible nucleus may become quite distinct. Other nuclei will immediately lose their indefinite outline by being surrounded by a clearly defined ring, making the nucleus appear at once larger, and doubly contoured. As healing progresses, the double border gradually grows together.

Evidence that a bone at some previous time showed signs of rickets may not be absent from the roentgenograms even when the disease has been healed for a long time and when the normal growth of the bone has carried the epiphyseal line considerably beyond the old site of the process. In these cases, a dense line may be seen crossing the shaft transversely at some distance from the growing end, this line marking the termination of the shaft at a time when the rickets was active, and having been formed by lime salts deposited at the onset of healing. In cases in which the disease has shown several periods of activity with intermediate healing, the shaft may be traversed by more than one of these lines. Now and again, when alternate periods of activity and healing have occurred with frequency and rapidity, the whole end of the bone may present a mottled, honeycombed appearance, due to the overlapping in different planes of the several epiphyseal lines.

PATHOLOGY OF RICKETS

In normal bone, the largest part of the epiphysis consists of a mass of undifferentiated cartilage cells. As the diaphysis is approached, the cells begin to swell and take on a more rounded form, and to be arranged in columns. The infiltration, with lime salts, of the intercellular matrix among the lower cells of these columns produces the epiphyseal line. The calcified intercellular substance serves to direct the marrow blood vessels against the rows of cartilage cells, and they are destroyed in an orderly fashion as the growth of the bone goes on. The calcified matrix is itself destroyed by osteoclasts and replaced by trabeculae through the activity of osteoblasts. The new bone is first laid down as osteoid tissue, which differs from mature bone only in a lack of lime salt deposits, but, in health, calcification is rapid, and only a narrow rim of osteoid is ever found. Growth in thickness is much slower and is carried on by subperiosteal osteoblasts. In the marrow cavity, the trabeculae are few in number and very loosely interwoven; while, in the cortex, they are numerous and thick, giving to it a dense and homogeneous appearance. It is important to keep in mind that the trabeculae are being continuously resorbed by osteoclasts and replaced in modified form by osteoblasts, so that the adult bone will finally be evolved in its permanent form.

In rickets, the primary fault lies with the process of calcification. The cartilage continues to grow at a normal rate; but owing to the

absence or irregularity of calcium deposition, the orderly destruction of the cartilage by the marrow elements and the conversion of the calcified intercellular substance into the shaft are interfered with. Diaphyseal elements, consisting of blood vessels and surrounding osteoid and connective tissue, are found invading the epiphysis in a more or less lawless fashion. The ultimate result is a wide area between the true epiphysis and diaphysis corresponding to the destroyed epiphyseal line and consisting of scattered areas of osteoid tissue, connective tissue, blood vessels and cartilage cells. This area has been termed the metaphysis. It is deficient and at times entirely lacking in lime salt deposits. In the shaft, the processes of resorption and deposition continue to go on as normally, but with this difference: the newly formed bone does not become ossified, but remains in the form of osteoid tissue, which thus comes to form a rim about the old trabeculae. The peri-

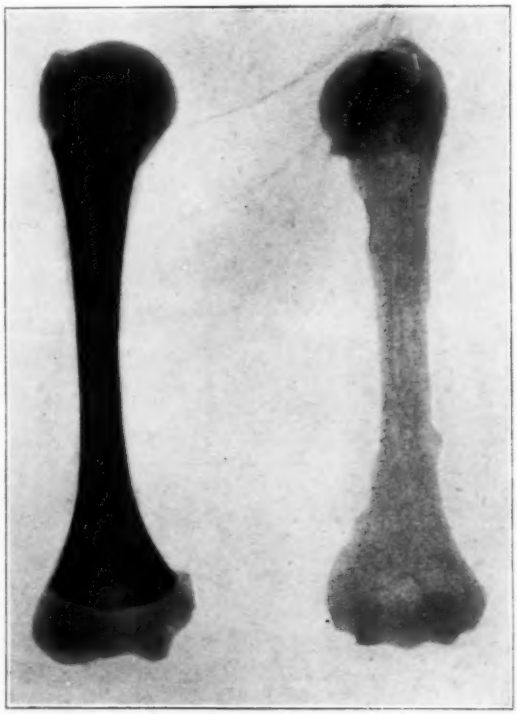

Fig. 1.—The left humerus of a full term infant after decalcification in nitric acid compared with the corresponding normal bone from the right side. The removal of the lime salts has destroyed the characteristic features of the bone, and the formerly dense shaft is even more permeable to the roentgen rays than the cartilage.

osteum as a rule is not altered, but occasionally there are signs of an active hyperplasia, with considerable thickening.

When healing begins, as Schmorl has shown, there first occurs a deposition of lime salts between the cartilage cells on the epiphyseal side of the metaphysis, where calcification normally occurs and presumably would have occurred had there been no rickets. As time goes on, the new line is broadened; the osteoid tissue in the metaphysis and in the shaft is ossified, and normality is regained. If at any time there

Fig. 2.—The two humeri of a full term infant: the one on the left normal, the one on the right after the removal of its organic and constituents with alkali. Except for the disappearance of the cartilaginous ends, and the slightly greater distinctness with which the individual lamellae have been outlined, there is strikingly little change.

is a recurrence of the disease, the new epiphyseal line will be broken through in numerous places by the again invasive marrow elements, and the line of calcification corresponding to the period of healing will be buried in the widening metaphysis. Occasionally, two, three or even more of these buried lines of calcification may be found, indicative of so many frustrated attempts at healing.

ANALYSIS OF SHADOW CASTING ELEMENTS

The foregoing description of the histologic findings will serve to point out the elements which go to make up normal and rachitic bones. An attempt has been made to determine which of these are responsible for the shadows in roentgenograms. In general, every tissue offers some obstruction to the passage of the rays; but since in life the bones are always surrounded by muscles, skin, etc., we are necessarily interested mainly in those elements which cast a shadow of greater or less intensity than the surrounding soft tissues, as only these will be distinguishable when analysis is attempted. It has already been mentioned that the cartilage of the epiphysis is generally invisible. Nor is it possible by roentgenograms to distinguish between undifferentiated cartilage and the proliferative zone, although in histologic sections the difference is marked. They are equally permeable to rays.

Fig. 3.—A section through the end of a bone, with marked syphilitic osteochondritis, stained with nitrate of silver, contrasted with the roentgenogram of the slice of bone from which the section was cut. The broad band of calcified intercellular substance (*a*) has cast an especially intense shadow.

It is quite generally stated that the greater density of the shaft is due to the presence of lime salts, as clinical experience teaches that lime salts wherever deposited will obstruct the roentgen ray. The calcified tuberculous kidney and the calcified plaques of arteriosclerotic vessels are familiar examples. To verify this, both humeri were removed from an infant with a normal skeleton. One of these was preserved in neutral formaldehyd,[1] the other was completely deprived of inorganic salts by the action of 5 per cent. nitric acid. Roentgenograms were then taken on one plate of the two side by side. Microscopic sections cut from the decalcified humerus showed that the histologic structure had not been changed by the action of the acid. The roentgenogram demonstrated beautifully that the increased density of the shaft is due entirely to the presence of inorganic salts. Indeed,

1. We have determined by pictures made before and after treatment with neutral formaldehyd that the fixing process does not alter the roentgen-ray picture.

the decalcified diaphysis seemed somewhat more permeable to the roentgen rays than the overlying epiphyseal cartilage.

The converse of this experiment was next attempted, to determine the part played by the organic component. For this purpose, two infantile humeri were again selected, one of them being preserved as before. The other was deprived of organic substances by a thorough boiling in a 5 per cent. solution of potassium hydroxid. After washing, the specimens were roentgenographed, and the second then placed in dilute acid, where, except for a slight cloud, it rapidly and entirely

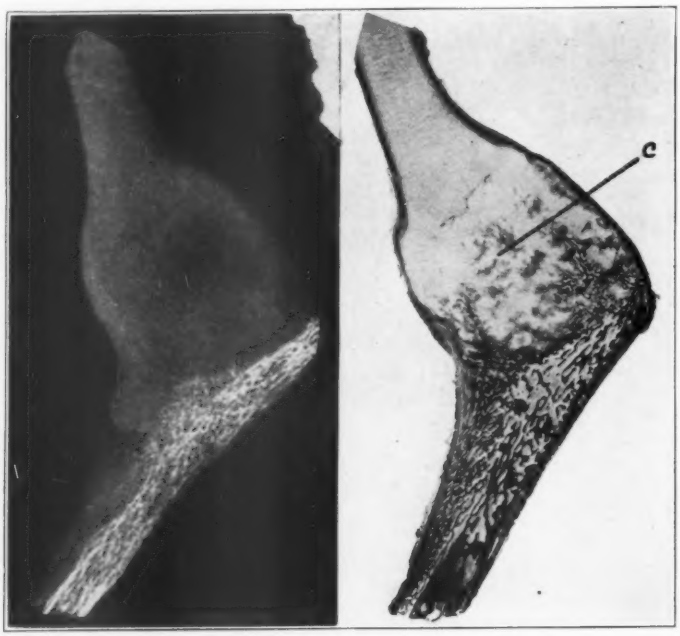

Fig. 4.—Section through a costochondral junction in a case of florid rickets stained by Mallory's connective tissue method and the roentgenogram of the slice of bone from which the section was cut. The abundant growth of connective tissue (*c*) in the metaphysis has not produced a corresponding shadow in the roentgenogram.

dissolved, showing that the removal of organic matter had been fairly complete. The alkali treatment had, of course, removed the epiphyseal cartilages, but, except for this, the roentgenographic pictures of the two bones were strikingly similar. On close examination only could it be made out that the trabeculae of bone were slightly more sharply defined after removal of the organic component.

These two experiments serve to emphasize the importance of calcified tissues from a roentgen-ray standpoint. Of these tissues, there

are two types: (1) calcified intercellular matrix and (2) calcified trabeculae. Both cast sharp shadows, but the shadow due to the former is especially intense. This is shown by the sharp line in which normal bone terminates, and by the new line which is formed when rickets begins to heal, but is much more vividly illustrated by the broad intense band which occurs in early hereditary syphilis. Careful comparisons of these more intense areas with the corresponding histologic sections will show that in each instance they are due to calcified intercellular substance. By cutting sections without decalcification and having them pictured by the roentgen ray, it has been shown that osseous trabeculae one-fifth millimeter in thickness cast a definite shadow and that trabeculae of one-half this thickness are often readily distinguishable.

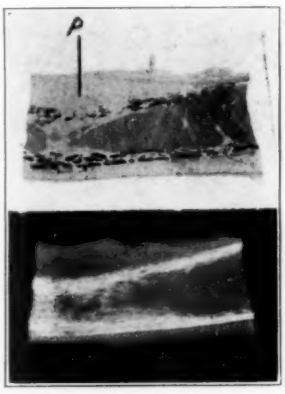

Fig. 5.—Section stained with hematoxylin, eosin and silver nitrate contrasted with a roentgenogram of the slice of bone from which the section was cut. Hyperplasia of the periosteum (*p*) has occurred on both borders of the shaft; the so-called rachitic periostitis. The thickened periosteum, composed almost entirely of osteoid tissue, does not cast a shadow with the roentgen rays.

It was next thought advisable to ascertain to what extent blood might influence the passage of roentgen rays. The rachitic metaphysis is considerably more vascular than any area in normal bone, and it was conceived that this might be a significant factor. An experiment was performed on a dog 5 months old, which was anesthetized with ether, the blood vessels to both hind legs being exposed by a midline abdominal incision. The right hind leg was congested with blood by injecting 5 c.c. of a 1 per cent. solution of sodium nitrite to dilate the capillary bed, and then ligating the common iliac vein on that side. When the congestion seemed complete, the artery also was ligated and the dog killed. The blood was completely washed from the left hind leg by allowing 3 liters of salt solution to run in the arterial and

out the venous side of the circulation. The whole lower half of the dog was then placed in formaldehyd for fixation, and later removed and the various bones from the two sides roentgenographed side by side. No essential difference in the pictures could be made out, showing that blood does not materially alter the permeability of bone to the roentgen ray.

Because of the nature of the rachitic process in which an excess of connective tissue is formed in the metaphysis, it has been possible to determine that this tissue does not noticeably affect the roentgen-ray picture. In one case, which is illustrated, a section through the costochondral junction, stained with Mallory's connective tissue stain, showed a luxuriant growth of connective tissue in the metaphyseal

Fig. 6.—Section of rachitic bone from the lower end of the tibia stained with Mallory's connective tissue stain, and the corresponding roentgenogram. In this case, the "fringe" produced by the invasion of the cartilage with marrow elements corresponds in extensiveness with the similar "fringe" in the roentgenogram. On microscopic examination, small bits of osseous tissue are found throughout the metaphysis.

zone, yet the roentgenogram of the slice of bone from which the section was cut gave no indication of this growth.

Likewise, osteoid tissue, which histologically is similar to other connective tissues, only more compact, seems to be a negligible factor from a roentgen-ray standpoint. In one marked case of rickets in which there had been considerable periosteal hyperplasia unaccompanied by any calcification, the thickened periosteum, composed almost entirely of osteoid tissue, was quite invisible in the roentgenogram. In other cases, not at all infrequent, scattered areas of osteoid tissue throughout the metaphysis have failed to show in the roentgenogram.

The rachitic metaphysis requires special consideration. Anatomically, it is a composite of cartilage, connective tissue, blood vessels containing blood, osteoid tissue and a variable amount of osseous

tissue. This last tends to be more abundant toward the diaphyseal border of the metaphysis. We are already familiar with the type of shadow the calcified tissue will cast, and this type will come into dominance as the diaphyses approach. But the epiphyseal border of the metaphysis is usually free from lime deposits. This border zone is somewhat more permeable to the roentgen rays than the adjacent cartilage and is often seen as a dark band between the indistinct termination of the shaft and the epiphysis. At first glance, one obtains the impression that the dark band is due to the proliferative zone of cartilage at the lower border of the epiphysis, but careful comparisons of sections with roentgenograms show conclusively that this is not the case. In many cases, this dark band may be indistinct or absent, seemingly owing either to imperfect roentgenograms or to varying

Fig. 7.—A slice of bone in which the full extent of the metaphysis is not indicated by the length of the "rachitic fringe." The dark transverse band, seen between the end of the shaft and the cartilage, is due to a portion of the metaphysis which is entirely free from osseous tissue.

permeability of this portion of the metaphysis. It was never so conspicuous in plates taken during life as it often was in the roentgenograms of slices of bone obtained after death.

The shadow cast by the marrow cavity is largely characterized by the interlacing osseus trabeculae which traverse it. When all lime salts are removed, as was shown by the acid-decalcification experiment, it is slightly more permeable than normal cartilage. The cortex owes its density to high concentration of calcium deposits. The periosteum is not visible. Even a thickened hyperplastic periosteum will not show unless the hyperplasia is accompanied by some calcification.

INTERPRETATION OF ROENTGENOGRAMS

We are now in a position to understand the meaning of the changes in the roentgenograms produced by rickets. The general rarefaction is due to the disturbance in calcification. Normal bone is composed,

roughly, of two parts inorganic matter to one part organic matter. In rickets, the proportions are reversed. But the osteoporosis associated with rickets differs in one important respect from that seen in most other diseases. In scurvy, in osteogenesis imperfecta, in the atrophy following nonuse and in the osteoporosis of old age, there is an actual atrophy of the lamellae. In rickets, the lamellae remain normal in size but are composed largely of osteoid tissue, and the central portion only is calcified. With healing, the density slowly returns to normal through gradual calcification of the osteoid rim. This begins centrally about the remaining osseous deposits and moves toward the periphery.

The epiphyseal cartilage, when the outline is visible, appears longer than in normal bone because it seems to embrace the upper portion of

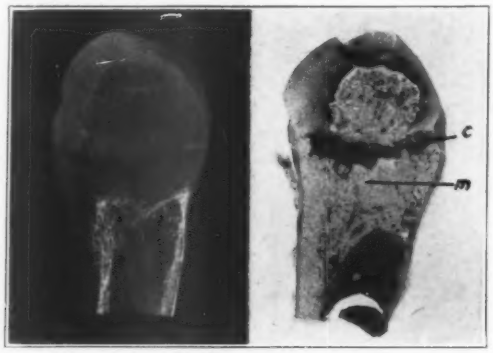

Fig. 8.—Roentgenogram and histologic section stained with hematoxylin and silver nitrate taken from the lower end of the femur of a rachitic colored child, 1 year old. The zone of proliferative cartilage (*c*) shows distinctly in the section as an irregular dark band and marks out the distal boundary of the metaphysis. The broad metaphyseal zone (*m*) has produced no corresponding shadow ("fringe") in the roentgenogram.

the metaphysis. When healing occurs, the initial deposit of lime salts in the lower border of the proliferative zone of cartilage marks sharply the boundary of the epiphyseal cartilage, and it at once appears shorter, though in reality there has been no change.

The fringe-like termination whereby the shaft gradually merges with the cartilage is the most characteristic feature of the roentgen-ray pictures. The marrow vessels which spring from the shaft to invade the cartilage, carrying with them surrounding areas of connective tissue, osteoid and fragments of osseous tissue, may be likened to so much luxuriant foliage sprouting from the end of the shaft of the bone. The connective tissue, corresponding to the leaves, does not leave a record on the plate, but the calcium deposits in the stems do. Therefore, the roentgenograms do not give a complete idea of the extent

of the invasion. This is well shown in sections stained by Mallory's method. When compared with roentgenograms, it can be seen that the fringe is more extensive in the former and reaches further toward the epiphysis. The extent to which the fringe-like termination in sections stained by Mallory's method will coincide with the similar appearing termination in roentgenograms depends largely on the presence of scattered lime salt deposits. In some cases, a most luxuriant growth of connective tissue will have absolutely no corresponding shadow in the roentgenogram. These we are inclined to regard as cases in which calcification ceased entirely after the onset of the disease. In other cases, there may be almost complete coincidence

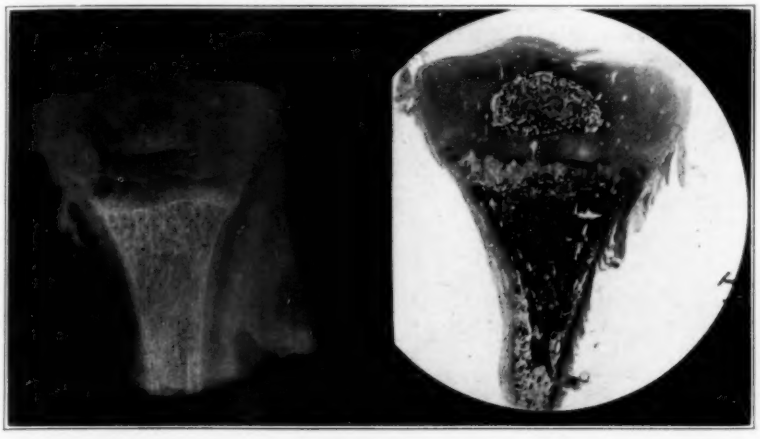

Fig. 9.—Roentgenogram and histologic section (stained with silver nitrate and hematoxylin) of a slice of bone taken from the upper end of the tibia in a rachitic child of 11 months, who had received treatment with cod liver oil for a period of one month. The section shows the new line of lime salts in the lower border of the epiphyseal cartilage and the lime-free hiatus which results at the end of the shaft. The roentgenogram shows shadows corresponding to the areas of calcification.

between the two fringes; and here we may consider the course of the disease as mild, with calcification never ceasing entirely and the duration roughly proportional to the length of the fringe. But in the usual case which we have described, the connective tissue fringe of histologic sections extends farther toward the epiphysis than the corresponding termination of the roentgenograms. This may be taken to indicate an insidious onset of the disease, with gradual but finally complete cessation of calcification.

In healing, the initial line of deposit in the proliferative cartilage lies just beyond the top of the connective tissue fringe. In roentgenograms, therefore, its onset is attended by a seeming increase in length,

and a hiatus is left between the new line and the shaft termination, which is gradually filled in as ossification brings about a slow return to normal.

Not infrequently, the roentgenograms will show a transverse line crossing the bone just below the beginning of the fringelike ending. This is due to the arrangement of the lamellae in that region, and probably marks the original end of the shaft before the onset of the disease.

The explanation of the cupped-out depression so frequently seen at the end of the shaft is forthcoming when we consider the firm elastic condition of the cartilage and the softened state of the rachitic bones. Because the bones are constantly pulled together by normal muscle tone and muscular activity, the end of the shaft mushrooms, spreading out along the lines of least resistance. The concavity is ordinarily distinct enough during the active phase of the disease, but is poorly outlined because of the indistinct termination of the shaft. In the phase of recovery, the new calcium deposits accentuate this appearance. The increased size of the epiphyses and the enlarged costochondral junctions are due partly to this mushrooming and partly to a thickening brought about by nature to meet the new functional demands, in accordance with the principle of Wolff's law. The bones are most deficient in lime salts at their growing ends and are therefore weakest at that place. Thickening takes place in order to bring added strength.

We have mentioned the distinctive laminated appearance of the cortex which may develop in the course of the disease and which shows plainly in the roentgenograms. This, too, may best be explained by the principles involved in Wolff's law. The new arrangement of the lamellae in the cortex of the bone, whereby the same amount of osseous tissue is spread over a greater area by means of a more loosely interwoven pattern, gives greater strength to the bone.

Now and again, a periosteal hyperplasia occurs in rickets, but the thickened periosteum does not cast a roentgen-ray shadow unless some calcification has taken place; that is, osteoid tissue formed by the periosteum is of the same density as the neighboring muscles. This explains why the administration of cod liver oil and the resulting return of calcification may be followed by the sudden appearance of a previously invisible periosteum.

The explanation for the changes in the epiphyseal centers of ossification are analogous to those for the alterations in the shaft. Invisibility or the degree of faintness depends on the amount of calcification. Growth occurs along the circumference of the nucleus, and the indistinct boundary here is exactly similar to that seen at the end of the

shaft. The roentgen-ray picture of the nucleus is smaller than the real nucleus because the peripheral sprouts of connective tissue do not cast a shadow. With the onset of healing, intercartilaginous calcium deposits immediately surround the nucleus, giving the double-contoured effect, so that in the roentgenogram it at once looks larger.

One more feature of the roentgenogram in the healing phase deserves special explanation. It has been noted that the new line which appears as the result of the resumption of calcification in the cartilage will frequently appear to be double, or in the form of an ellipse. The double line is really the boundary of the surface of the new plane of ossification. Why the boundary of the plane should cast a more intense shadow than the central portion is made clear by a study of the histologic sections, in which it may be seen that the new epiphyseal line is broader and more completely calcified at the periphery than in the central portion.

SUMMARY AND CONCLUSIONS

The only element which constantly casts a shadow in roentgenography of rachitic bones seems to be calcium, in the form in which it normally appears in bone. Those tissues which, normally calcified, have become decalcified either leave no record or do so only by casting a negative shadow. These simple facts, combined with an understanding of the pathology of rickets and its variations, enable us not only to explain the shadows which characterize rickets roentgenographically, but also to predict with a fair degree of accuracy, from the examination of a roentgenogram, the actual histologic alterations.

SICKLE CELL ANEMIA

REPORT OF TWO CASES IN CHILDREN, WITH NECROPSY IN ONE CASE

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J. B. Herrick,[1] in 1910, reported a peculiar dyscrasia characterized by severe anemia, with the occurrence in the blood of elongated and sickle-shaped erythrocytes. Three instances of this condition have since been described, one by R. E. Washburn;[2] one by Cook and Myer,[3] and one by V. R. Mason.[4] Emmel[5] further studied the blood of Cook and Myer's case, demonstrating the existence of phagocytosis of the erythrocytes by large mononuclear leukocytes in the peripheral circulation. He also pointed out the fact that when sealed sterile preparations of the fresh blood were allowed to stand at room temperature for varying periods of time, many of the circular erythrocytes underwent transformation into elongated and sickle shapes similar to those seen in the freshly drawn blood. Furthermore, he showed that the blood of the patient's father, though normal to all appearances when drawn, underwent similar changes on standing. Guthrie and Huck[6] refer to a fifth case of sickle cell anemia, as yet unreported. Dresbach[7] and Bishop[8] have called attention to the occurrence of elliptic cells in human blood in patients with no other evidence of abnormality. The blood picture in their cases was, however, quite different from that in the others referred to.

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4. Mason, V. R.: Sickle Cell Anemia, J. A. M. A. **69**:1318 (Oct. 14) 1922.
5. Emmel, V. E.: A Study of the Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, Arch. Int. Med. **20**:586 (Oct.) 1917.
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7. Dresbach, M., quoted by Bishop, F. W.: Elliptical Human Erythrocytes, Arch. Int. Med. **14**:388 (Sept.) 1914.
8. Bishop, F. W.: Footnote 7.

A study of the blood pictures and clinical findings in the reported cases and in our two cases leads us to the belief that sickle cell anemia is probably a definite clinical entity. Also we are quite convinced that the condition is familial. An analysis of the symptoms and signs common to the reported cases (Table 1) gives the following information. All cases have occurred in negroes or mulattoes, with no special selection for sex. Evidences of severe anemia existed in every case. A definite and characteristic blood picture was present in all cases. Scleral discoloration, recorded as "a greenish tinge" or "tinge of yellow" was constant. Splenic enlargement was absent in all cases except our Case 2. (This patient had a severe malarial infection seven months before admission to the hospital.) Leg ulcers, which were present in all four reported cases, were absent in our two cases. Severe recurrent abdominal pain was mentioned by every patient except Cook and Myer's. General glandular enlargement, arthritic pain with occasional swelling of joints, edema of feet and ankles, cardiac enlargement and urinary abnormalities were not all present in every case, and these symptoms are so frequently present in cases of prolonged secondary anemia that we feel they are to be interpreted as manifestations of the anemia present in the cases under discussion rather than symptoms of sickle cell anemia.

As regards evidence pointing to a congenital or familial pathogenesis in this condition, the following points may be noted. Presumptive evidence of anemia, namely, general weakness, indisposition to exertion and dyspnea, dated back to childhood in the cases of Herrick, and Cook and Myer. In Washburn's and Mason's cases, they dated from the patients' earliest recollection. In our Case 1, weakness began at the age of 2 years. In the cases of Herrick and Mason, no family history of significance could be elicited. In Washburn's case, the family history carried a high child mortality, four sisters and four brothers having died in infancy and childhood from undetermined causes except in the case of one sister who died of "brain trouble." Cook and Meyer gave special attention to the family history, stating that all the children, two brothers and two sisters, had suffered from severe anemia. The case of one of the girls was reported. The sister died at the age of 22, of tuberculosis. It was stated that, at the age of 5, she had grown thin and sallow and had had pains in the extremities. Both the brothers died of anemia. Dr. E. W. Sanders saw the children and made the following notation: "I found the children the victims of a severe anemia. One of them died, and I then lost sight of the family."

In the four reported cases, the blood of relatives of the patient was examined in only one instance. The blood of the father in Cook and Myer's case was normal on being drawn, but "sickled" after standing

TABLE 1.—*Summary of Chief Points of Interest in Cases of Sickle Cell Anemia*

	Herrick's Case	Washburn's Case	Cook and Myer's Case	Mason's Case	Case 1	Case 2
Race	Negro	Negro	Mulatto	Negro	Negro	Negro
Sex	Male	Female	Female	Male	Male	Male
Age	20 years	25 years	21 years	21 years	5 years, 7 months	6 years
Presumably onset of symptoms referable to anemia	At age of 10 years, following attack of yaws	"Weak all her life"	Ulcer of leg at age of 5 years	Patient was weak and sickly as far back as he could remember	At 3 years of age	At age of 6 (present illness)
Family history	Father died of accident; mother and three brothers healthy	Father in bad health for many years; mother died of "rheumatism"; four sisters and four brothers died in childhood; causes of death unknown except "one sister died of brain trouble"	Father living, condition of health not mentioned; mother died of cancer; two brothers said to be the victims of severe anemia of which one died at age of 7, the other at age of 17; one sister, who died at 22 of tuberculosis, began to grow thin and sallow at age of 5 and suffered with pains in the extremities	Fragmentary; no evidence of others in family being affected	Paternal grandfather living and well; paternal uncle living and well; maternal grandparents, no information; mother living and well; three brothers, two apparently healthy, one weak, dyspneic, suffers from abdominal pains and articular pains; one sister died at age of 5 days from hemorrhagic disease of newborn; one sister 10 months old, living and well	No information as to grandparents; father and mother living and well; nine siblings all living and well
Leg ulcer	At age of 10	At age of 20	At age of 5	At age of 21	No ulcer	No ulcer
General glandular enlargement	Present	Present except axillary glands	Not mentioned	Present	Present	Present
Scleral discoloration	A tinge of yellow	A greenish tinge	A greenish tint	A peculiar greenish hue	Greenish yellow	Greenish yellow
Dyspnea on exertion	For about 1 year	For five years	Present, duration not mentioned	Not mentioned	For two years	Not present
Cardiac enlargement	Present	Present	Not mentioned	Present	Present	Present
Splenic enlargement	Absent	Absent	Absent	Absent	Absent, spleen weighed 8 gm.	Present (malaria, 7 mo. previously)
Abdominal pain	Epigastric pain	Pain and tenderness over spleen	Not mentioned	Pain in upper abdomen	Upper abdominal pain	Epigastric pain with vomiting
Muscle and joint pains	Muscular and arthritic pains	No pains, but swelling of wrists and ankles	Rheumatic pains for years	Not mentioned	Pains in all large joints	Absent
Urinary findings	Albumin, casts, trace of bile	Pus and casts, bile present	Not mentioned	Albumin, casts, bile present	Casts, urobilin present	Casts, urobilin present
Wassermann reaction	Not in use	No record	Negative	Negative	Negative	Negative
Malaria	Negative	Negative	Negative	Negative	Negative	Negative
Stools	Negative	Negative	Negative	Negative	Negative	Negative
Blood culture	No record	No record	No growth	No growth	Negative	Negative
Sickle cells or "latent sickling" in blood of other members of family	No examination	No examination	Father's blood showed "latent sickling"	No examination	Paternal grandfather, father and one brother show "latent sickling," two brothers have sickle cells	Father, mother and two sisters have "latent sickling"; no other members of family examined

for variable periods of time at room temperature. Guthrie and Huck [6] refer to the presence of sickles in the blood of a number of relatives of their patient. In the family of our Case 1, the paternal grandfather, the father and one brother showed "latent sickling" as described by Emmel;[5] while two brothers presented the typical blood picture of sickle-cell anemia. One of these brothers, in fact, presented the entire group of symptoms which we have outlined above, to a more striking degree than the patient himself. All the members of this family who presented the sickle-cell phenomenon had greenish yellow sclerae (quite different from the "muddy" discoloration so common in negroes), general glandular enlargement and absence of splenomegaly, and three gave a history of recurrent abdominal pain. In the family of our Case 2, both the father and mother showed "latent sickling," as did two of the sisters. All showed the characteristic scleral discoloration and general glandular enlargement. No other members of the family could be examined owing to superstitious fears aroused by our interest in their blood.

As all the reported cases of sickle-cell anemia have developed in adults and no necropsy has been recorded in the literature, we present in considerable detail two cases occurring in children.

REPORT OF CASES

Case 1.—*History.*—A. C., a boy, negro (pure blood), aged 5 years and 7 months, entered the University Hospital, Aug. 23, 1922, complaining of general rigidity of body, arms and legs, with frequently recurring painful tonic spasms, and frequent attacks of abdominal pain localized in the epigastrium. The grandfather on the father's side was living and apparently well. The grandmother died from an unknown cause many years ago. There were no data obtainable as to the maternal grandparents. The father and mother were living and healthy. Both had had malaria in childhood. There was no history of syphilis. There had been one miscarriage at three months, the second pregnancy. Of five siblings, one sister (aged 5 days) died of hemorrhagic disease of new-born (bled to death from navel). A brother, aged 11, was in good health but tired easily and was somewhat breathless after exertion. A brother, aged 8, was not well. Four years previously, he had many swollen joints, with pain and tenderness, tired easily, was short of breath on slight exertion and had frequent attacks of abdominal pain. A brother, aged 4, was apparently well, and a sister, aged 20 months, was well. There was no history of usual diseases believed to show familial tendency.

A. C., a full term baby, born with normal delivery, weight 8 pounds (3,630 gm.), developed normally throughout infancy. He was breast fed for one year, but after the sixth month was given additional feeding of almost anything on the family table, notably cabbage "pot liquor." Since the age of 1 year, he had eaten practically everything he could lay his hands on, including dirt, plaster, clay, paint off the side of the house and grass. He frequently chewed shoe strings. In spite of these exceptional dietary vagaries, he was, so his mother said, a strong, healthy child up to 2 years of age. There was no history of measles, pertussis, chickenpox, smallpox, scarlet fever, diphtheria, congenital syphilis or ground itch.

Two years before, an "irregular" physician, without physical examination or blood examination, stated that the patient had malarial fever. He was in bed about one month, and was at times delirious, at other times stuporous. After he was out of bed, his mind was clear, but his left arm and left leg were weak. The left arm was spastic and flexed at the elbow; the left leg was spastic and tripped him in walking (probably poliencephalitis). After being up about two weeks, he began to vomit and had pains in upper abdomen. A few days later, his feet began to swell. Pains developed in the shoulders, elbows, wrists, knees and ankles, and were followed in a few days by swelling in the joints. He soon began to complain of shortness of breath on exertion. These symptoms had all been present more or less constantly up to the onset of the present illness. For the past six months, the mother said, the child had complained at times of pains in the ears and difficulty in hearing, although there had never been any discharge from the ears.

Six weeks before, the patient began to complain of more than usual disability; wished to lie down all the time; had frequent vomiting, with almost constant high abdominal pain, and was markedly constipated. Two weeks later, the stiffness of the joints on the left side of the body became more marked, all the large joints being involved. Following this, the corresponding joints of the right side gradually became affected, and, for the past four weeks, the patient has suffered great pain when turned in bed. Two weeks ago, there was a sudden onset of painful tonic spasms, at first occurring every six to eight hours but increasing in frequency until, at the time of examination, there was one nearly every hour. These were frequently precipitated by moving or handling the patient. There had been marked mental dulness since the onset of the spasms. There had been no trismus.

Physical Examination.—The temperature was 98 F.; pulse, 102; respiration rate, 20; blood pressure, 118 systolic and 50 diastolic.

The patient was poorly nourished and underdeveloped. When not in tonic spasm, he lay quietly in bed, apparently in considerable pain. The mental condition was poor, and one gained the impression that this was a case of meningitis. The forearms were flexed on the arms, the fingers, flexed over the thumbs; the legs were extended, and the entire left side exhibited more spasticity than the right. The skin was dry and loose.

The head was normal in shape and size, with no exostoses or other bony prominences. The fontanels were closed. The eyes showed moderate exophthalmos, but there is no gross evidence of disturbance of the extra-ocular muscles. The conjunctivae were pale, and the sclerae showed a uniform deep greenish-yellow discoloration. The pupils were round, not dilated, equal in size and reacted to light. Ophthalmoscopic examination revealed no abnormalities aside from marked anemia. The ears were negative on external and otoscopic examination. The nose showed nothing abnormal. The mucous membranes of the mouth were very pale; the tongue was coated; the teeth showed caries, and the tonsils were large, with many large crypts. The pharynx was negative.

Examination of the neck revealed marked enlargement of the posterior cervical glands. The thyroid was negative.

The axillary, epithrochlear and inguinal glands were enlarged and firm.

The thorax showed normal conformation and equal expansion. The respiratory movements were good. The lungs were negative throughout on percussion and auscultation.

Examination of the heart revealed: apex beat in fifth interspace, 1.5 cm. outside the midclavicular line; no shocks or thrills over the precordium; relative dulness extending 3 cm. to the left of the midclavicular line in the fifth interspace, 2.5 cm. to the right of the sternal margin in the fourth interspace. The heart sounds in the mitral area were of fair quality. There was a prolonged blowing systolic murmur audible over the entire precordium, with intensification in the mitral and pulmonic areas. The pulmonic second sound was accentuated.

The abdomen appeared to be normal. The liver, spleen and kidneys were not palpated. There was no rigidity or muscle spasm.

The genitalia and the extremities were negative.

Tests of the reflexes revealed: biceps, triceps and periosteoradial, hyperactive, more on the left than the right; abdominal and cremasteric, present; knee jerks and ankle jerks, markedly exaggerated, with no clonus; Kernig, positive; Babinsky, Oppenheim and Gordon, negative; Trousseau and Chvostek, negative. There was no opisthotonus.

During a spasm, there was moderate retraction of the head, the jaws were fixed and the arms were held close to the body, with the fore arms and hands tightly flexed. The trunk muscles were rigid without true opisthotonus. The thighs and legs were rigidly extended.

Laboratory Examinations.—The urine was clear, amber, with a specific gravity of 1.005; acid, and reacting negatively to tests for albumin, sugar,

Fig. 1 (Case 1, A. C.).—Fresh blood preparation; × 600.

acetone and diacetic acid and bile. The test for urobilin was strongly positive. Microscopic examination revealed a few hyaline and granular casts.

The stool was negative for blood, ova and parasites.

Blood examination revealed: erythrocytes, 1,328,000; hemoglobin, (Dare) 25 per cent.; leukocytes, 64,000; color index 0.9; differential count: 1,000 cells; neutrophils, 78.1 per cent.; eosinophils, 0.9 per cent.; basophils, 0.1 per cent.; large mononuclears, 2.6 per cent.; small mononuclears, 13.5 per cent.; large lymphocytes, 0.9 per cent.; transitionals, 1.9 per cent.; myelocytes, 0.5 per cent.; myeloblasts, 0.4 per cent.; unidentified, 0.7 per cent.

Particular interest centered around the blood. While making the red count, it was noted that a number of the erythrocytes in the counting chamber were tenuous, oat shaped and "sickle" shaped. Examination of a stained smear confirmed the impression already formed of the character of the blood. The salient characteristics of the erythrocytes as seen in the stained smears were as follows: 1. There were a large number (about 20 per cent.) of sickle-shaped and elongated red blood cells. There was great variation in the size of these cells, some being so small as to suggest fragments of cells, others attaining a length of from 13 to 14 microns and a width of from 2 to 4 microns. These erythrocytes, when narrow, stained deeply and evenly; when

wide, there was often a pale area in the middle, comparable to that seen in the red cells in secondary anemias. 2. The approximately normal shaped cells, which made up four fifths of the total red count, presented the appearance which is associated with severe secondary anemia. There was marked anisocytosis, the microcytes as a rule staining deeply, while the macrocytes and normocytes tended to be pale, with marked central pallor. There were many cells showing diffuse basophilia. Punctate basophilia was not noted. 3. Nucleated red blood cells were seen in all preparations that were examined. As a rule, these were typical normoblasts. A few intermediates with megaloblastic nuclei were seen, but no typical megaloblasts. No nucleated sickle cells were seen.

In practically all of the stained smears, there were occasional large mononuclear leukocytes which had engulfed erythrocytes. The number of these phagocytes varied greatly from day to day. On some occasions, cells were seen which had as many as three red cell inclusions.

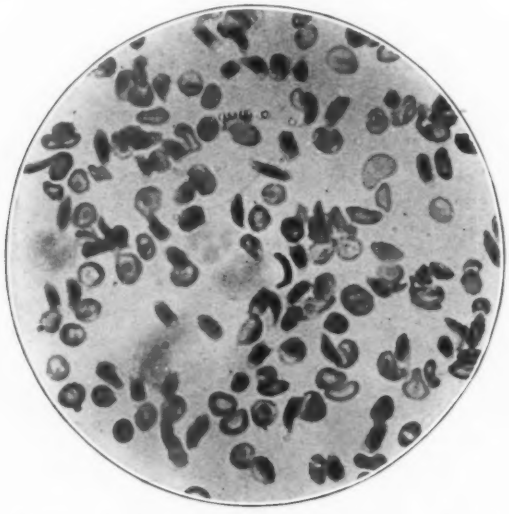

Fig. 2 (Case 1, A. C.).—Stained blood smear; × 600.

The blood platelets presented no abnormalities in number or structure. The leukocytes presented some points worthy of note. Many of the neutrophils showed an extraordinary degree of lobulation of the nuclei, seven and eight lobes being seen in many of them. In addition, many of them presented the nuclear excrescences noted by Emmel.

The absolute number of eosinophils was much increased, although the percentage ratio was not above normal. No unusual lobulation of the nuclei of the eosinophils was noted, nor were there any nuclear excrescences. The number of immature leukocytes of myelogenous origin was not greater than would be expected in a leukocytosis of this grade in a child of 6.

The fresh blood showed the same degree of sickling and anisocytosis that was observed in the stained smears. It presented other peculiarities which will be described at length below. Smears of the patient's blood stained with brilliant cresyl blue showed from 15 to 24 per cent. of reticulocytes on various occasions. It was noted that only a small number of the sickle cells showed reticulation. The resistance of the erythrocytes to hypotonic salt solutions was tested and found to show no variation from the normal. Hemolysis began at 0.45 and was complete at 0.26.

The serum of this patient when collected with all precautions against hemolysis was a brilliant lemon yellow. Unfortunately, no effort to determine urobilin in the serum was made.

The blood sugar was normal, 100 mg. per hundred cubic centimeters of blood. The Wassermann reaction was negative on two occasions. The patient's blood belonged to Group IV (Moss classification). The two transfusions which he received were without effect on the blood picture and were unaccompanied by any objective signs of reaction.

Lumbar puncture was done on the day of admission and again four days later. The fluid was clear on both occasions; there was no globulin, and the cell count was four and six. The Wassermann and colloidal gold tests were negative.

Course in Hospital.—Treatment was directed toward the recurrent spasms, and an effort was made to improve the general condition by the transfusion of blood. The temperature did not go above 102 F. at any time. The patient's condition grew steadily worse, without any satisfactory cause for the convulsions being discovered. Death occurred during a spasm on the eighth day under observation.

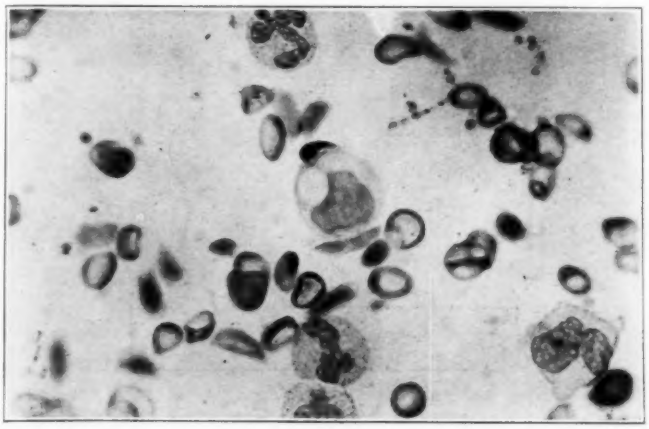

Fig. 3 (Case 1, A. C.).—Stained blood smear, showing large mononuclear phagocyte with red cell inclusion; × 900.

Necropsy Findings (Dr. Lichenstein).—Necropsy was performed two hours after death. The body was 100 cm. long; weight 20 kg. The skin was smooth. Rigor was absent. The pupils were moderately dilated, even and equal. The sclerae were decidedly greenish-yellow. The visible mucosa was extremely pale. Examination of the extremities revealed nothing noteworthy.

The thymus gland was disproportionately large for the age. Both pleural cavities contained a few slight adhesions. Examination of the lungs revealed nothing noteworthy besides pallor. The pericardial cavity contained a slight excess of clear fluid. The heart was pale, and was increased nearly twice in size, particularly from an hyperthrophy of the left side. The right side contained clotted blood. Examination of the endocardium, the valves and the aorta revealed nothing unusual. The heart weighed 120 gm.

The liver extended 5 cm. below the costal margin, and was large, pale and somewhat greasy. There were no apparent changes in structure. The weight was 690 gm.

The spleen which was very small and was increased in consistency, measured 5 by 3 by 1 to 2 cm. Weight was 7.9 gm. The malpighian bodies were barely visible. The pulp was diminished, and many small dark red blotches were scattered throughout.

The pancreas measured 15 by 3 by 2 to 3 cm. There were no gross changes.

The kidneys were also increased in size, pale, considerably increased in consistency and finely scarred over their surfaces and throughout the cortex. The cut surface was rather cloudy and after fixation in formaldehyd a fine yellowish red stippling was seen throughout the cortex and the columns of Bertini.

Examination of the stomach, intestines and genitalia revealed nothing noteworthy. The mesenteric lymph nodes were enlarged from hyperplasia. The bone marrow from femur and ribs was bright red and of normal consistency.

Microscopic Notes (Dr. Lamar).—Liver: The cords were rather swollen and the cells more granular than usual and poorly defined in outline. There were numerous small scattered areas of fine dark brown pigmentation of the liver cells, apparently bile imbibition.

Fig. 4 (Case 1, A. C.).—Spleen; actual size.

Spleen: The capsule was slightly thickened and uneven from an occasional depression; the trabeculae were conspicuously large; the parenchyma was much reduced in amount, and the malpighian bodies were inconspicuous, ill-defined and distorted in outline. The blood, of which there is much, was most unevenly distributed in large and smaller areas of extreme congestion where the parenchyma was reduced. Besides, there were many small and large actual hemorrhages scattered throughout; some recent, others older, and the pigmented scars of others still older (Berlin blue reaction). To summarize, the spleen presented congestion, hemorrhages, scarring and marked atrophy (aplasia?).

Kidneys: The kidneys showed alike an uneven capsular line from numerous small depressions. The glomeruli were strikingly prominent and distended by blood, much of which was agglutinated. The nuclei in some glomeruli were increased twice in number, and there was pericapsular fibrosis in some glomeruli. Many of the convoluted tubules were dilated; most of them contained a granular precipitate, and a few contained casts. Generally, the epithelial cells showed cloudy swelling. Here and there, there were necrobiotic changes and occasional desquamation. Many epithelial cells, in smaller and larger groups throughout the sections, contain much fine and coarsely granular yellowish brown pigment. Indeed, the cells of some tubules were laden with this pigment, which does not give the iron reaction.

Beneath the capsule and scattered elsewhere throughout the section, even to some extent in the medulla, were small areas of recent fibrosis where some tubules were lacking and others were compressed. About some of these areas were small accumulations of mononuclear and polymorphonuclear leukocytes.

Mesenteric lymph nodes: These showed much diffuse hyperplasia.

Bone marrow: The femur contained a large number of sickle-shaped red blood cells, often in large clusters between the capillaries and sometimes within them. There was much brownish black pigment in fine and coarse granules, mainly extracellular, but also, to some extent, within large mononuclear cells.

In all the various sections of the organs, many sickle-shaped red blood cells were seen within the capillaries.

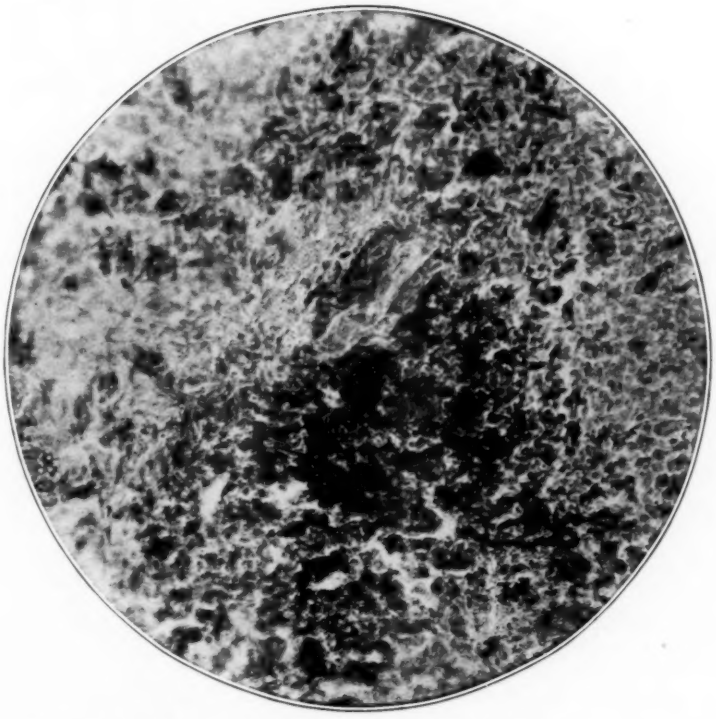

Fig. 5 (Case 1, A. C.).—Section of spleen, showing fresh hemorrhage; × 400.

Pathologic diagnosis: A diagnosis was made of emaciation, anemia, parenchymatous nephritis (subacute); hypertrophy of heart, atrophy or aplasia of spleen, repeated hemorrhages, fibrosis; pigmentation of sclerae; pigmentation, iron-free, of kidneys; enlarged thymus; mesenteric lymphatic hyperplasia; slight pleural adhesions; sickle-shaped red blood cells.

Smears from the marrow of ribs and femur were stained with Wright's stain. These preparations were of special interest. The white cells presented no particular abnormalities aside from those compatible with increased activity of the marrow, myeloblasts and immature myelocytes being present in large numbers. The erythrocytic elements, however, were strikingly abnormal and differ from any that we can find described. The abnormal types of red blood cells can be divided into three groups:

1. Sickle and oat shaped cells similar in all respects to those found in the peripheral blood, but relatively much more numerous. These showed varia-

tions in size even more pronounced than those seen in blood smears, and polychromatophilia was frequent. Erythroblasts presenting these forms were common. The nuclei of these nucleated sickle cells were uniformly of the dense normoblastic type and varied much in size. Usually, the nucleus was round and occupied the middle of the cell. Occasionally, forms were seen (Fig. 7*a*) in which the nucleus was elongated in the direction of the long axis of the cell.

2. Filiform erythrocytes, the length of which was six to twenty times the width. These cells presented the most bizarre forms and the greatest variation in size (Fig. 8). Some were so small as to suggest bacillary forms. These were probably fragments. Many were between 10 and 15 microns long with a diameter of 0.5 micron (Fig. 7*c*). The most striking types were the extremely long forms running up to 40 microns in length, varying in width from 1 to 5 microns. Many of these large forms presented enlargements at one end, giving them a club shape (Fig. 9). Others were larger at both ends

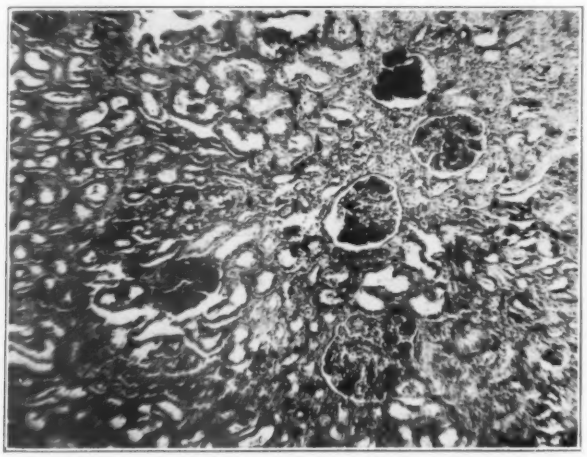

Fig. 6 (Case 1, A. C.).—Section of kidney cortex.

than in the middle. Still others showed excrescences at various points. These filiform cells occurred singly and in clusters. Occasional groups having a radial arrangement were seen. These cells were the most striking feature of the picture, forming a network over the entire smear. It was thought at first that trauma might have to do with their extreme tenuosity, but sections showed masses of the same type of cells in the intercapillary spaces.

Nucleated cells corresponding to these forms were of frequent occurrence (Figs. 7, 8 and 9). The nuclei of these usually occurred in or near one end of the cell, and were surrounded by a thin layer of cytoplasm. Nuclear extrusion, possibly the result of trauma, was a frequent phenomenon. The nuclei of these cells too were always of the normoblastic type, and usually very dense.

3. Erythrocytes and erythroblasts of no fixed shape or size. These were quite common, and only a poor idea of their variety is given by the figures. Some were large, as much as 20 microns in their greatest diameter, and in shape suggested masses of hemoglobin-containing tissue torn away from a mother lump. These large cells were frequently very irregular in staining qualities.

Nucleated forms corresponding to these were seen. A few presented the megaloblastic type of nucleus but the majority were normoblastic.

These abnormal forms by no means made up the entire erythrocytic content of the marrow. All the normal types of erythroblasts were present in large numbers, and about 60 per cent. of the erythrocytes were circular in outline but showed great variations in size.

Smears from the splenic pulp were also stained with Wright's stain. The only striking abnormality noted was the preponderance of sickle cells. From 50 to 60 per cent. of the red cells present were sickle or oat shaped. It is of interest that no evidence of phagocytosis of red cells was seen in any of the large mononuclear elements from the spleen.

CASE 2.—*History.*—R. R., boy, negro (pure blood), aged 6 years, entered the University Hospital, Feb. 9, 1923, complaining of headache, pains in the stomach, general weakness and jaundice. The grandparents were all dead, of unknown causes. The father, aged 40, and the mother, aged 38, were living

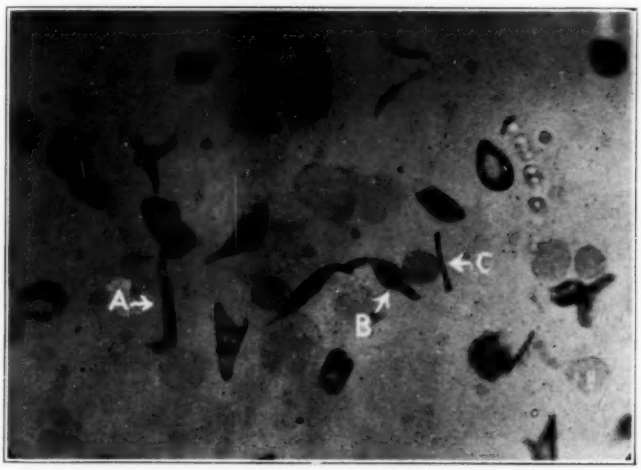

Fig. 7 (Case 1, A. C.).—*a*, sickle cell with elongated nucleus; *b*, bizarre erythroblast of spindle type; *c*, minute filiform erythrocyte.

and well. Both had had malaria repeatedly. There was no history of syphilis. Four brothers and five sisters were all living and well. There were no miscarriages. No history was elicited of the usual diseases believed to indicate a familial tendency.

The patient was a normal full-term baby, of a normal delivery, breast fed for ten months and then bottle fed, with the addition of various articles of diet. He was always perfectly well up to August, 1922, at which time there was a severe attack of malaria for which the patient was treated in the outpatient department. Plasmodia were found at this time, but no note was made of any abnormality of the blood.

The present illness began three weeks before, with headache and recurring attacks of abdominal pain referred to the epigastrium and left hypochondrium. There was no constipation or diarrhea. Headache had been constant. Attacks of abdominal pain occurred at intervals of two or three days, often accompanied by vomiting. Three days after onset, the mother noticed that the sclerae were slightly yellow. This jaundice had increased only slightly since. There had been no itching of the skin. There had been no dyspnea, but extreme lassitude.

Physical Examination.—The temperature was 101.4 F.; pulse, 120; respiration rate, 28; blood pressure, systolic 100, diastolic, 40. The patient was of good bony and muscular development and fairly well nourished. The skin was "gingerbread" color, with a definite suggestion of jaundice, particularly on the palms and soles. There was no rash. Slight edema of the ankles was noted. There was no evidence of rickets or congenital syphilis.

The head was of normal contour. The hair was sparse for a negro and had a peculiar reddish cast. There was no tenderness over the mastoids. The ears were normal on external and otoscopic examination. The eyes showed nothing abnormal except a very marked greenish yellow discoloration of the sclerae. The mucous membranes were very pale. The teeth were good; the tongue was pale and slightly coated; the tonsils were large but not inflamed.

The neck showed nothing abnormal. The glands, cervical, axillary, epitrochlear and inguinal, showed marked enlargement. The thorax was well

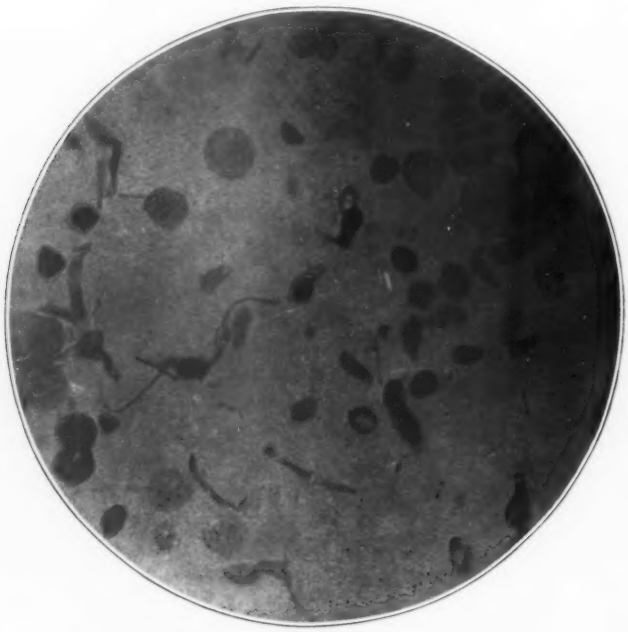

Fig. 8 (Case 1, A. C.).—Smear from bone marrow, showing various types of abnormal erythrocytes.

formed. The left costal margin flared slightly as compared with the right. The respiratory movements were good. The lungs were resonant throughout on percussion, but on auscultation there are very many moist râles of all sizes over both sides of the back, more numerous as the bases were approached. There were no significant changes in the breath sounds.

Examination of the heart revealed the apex beat in the fifth interspace in the midclavicular line. No thrill or shock was noted. Dulness extended 3 cm. outside the nipple line on the left. There was no increase on the right. The sounds were of fair quality. There was a loud blowing systolic murmur at the apex; and over the pulmonic areas, the pulmonic second sound was quite loud.

The abdomen was distended in the upper portion, where the liver was felt four finger-breadths below the costal margin, and the spleen on the left side

could be felt two finger-breadths below the costal margin. The spleen was hard, its edge thick and round. The kidneys were not felt. Examination of the genitalia revealed nothing noteworthy.

The reflexes were all normal.

To summarize: Jaundice, hypertrophied tonsils, physical signs of bronchitis, enlarged heart with systolic murmurs at mitral and pulmonic areas, marked enlargement of liver and spleen and severe anemia were noted.

Laboratory Examinations.—The urine was dark brown, clear, acid, with a specific gravity of 1.010, and negative for albumin sugar, acetone and diacetic acid and bile. Tests for urobilin were strongly positive. The stools were negative for blood, parasites and ova. Blood examination revealed: erythrocytes, 1,544,000; hemoglobin, 38 per cent. (Dare); leukocytes, 20,000; color index, 1.2; differential count (500 cells): neutrophils, 33.0 per cent.; eosinophils,

Fig. 9 (Case 1, A. C.).—Smear from bone marrow, showing club-shaped erythroblast.

2.2 per cent.; basophils, 0.6 per cent.; large mononuclears, 9.0 per cent.; small mononuclears, 48.6 per cent.; large lymphocytes, 0.8 per cent.; transitionals, 4.0 per cent.; myelocytes, 0.8 per cent.; unidentified, 0.6 per cent. Seventy nucleated red cells were seen. The platelets were normal in numbers and size.

The blood smear presented the typical picture of sickle-cell anemia. Twenty-seven per cent. of the erythrocytes were sickle-cells (Fig. 10). Two nucleated sickle-cells were seen. There was no evidence of malaria. The fresh blood showed the same characteristics as the smears, together with other peculiarities which will be described below.

The smears stained with brilliant cresyl blue showed 34 per cent. reticulocytes. The resistance of the erythrocytes to hypotonic salt solutions was normal. Hemolysis began at 0.45 and was complete at 0.24.

The serum was a deep canary yellow when collected with all precautions against hemolysis. The blood sugar was normal. The Wassermann reaction was negative. The patient's blood belonged to Group II (Moss classification).

More detailed examination of the stained smears of the blood confirmed the first impression that it presented the typical picture of sickle cell anemia. The variations in size and shape were the same as in Case 1. Phagocytes containing erythrocytes were somewhat more numerous in the blood than in that of Case 1, and on the first day in the hospital the smears showed several nucleated cells presenting the characteristic sickle shape and deep staining reaction. Nucleated sickle cells have not been described in any of the reported cases and were not found in the peripheral blood of our Case 1.

This patient remained in the hospital for eleven days, during which time many tests of the blood were made. There was no significant change in the

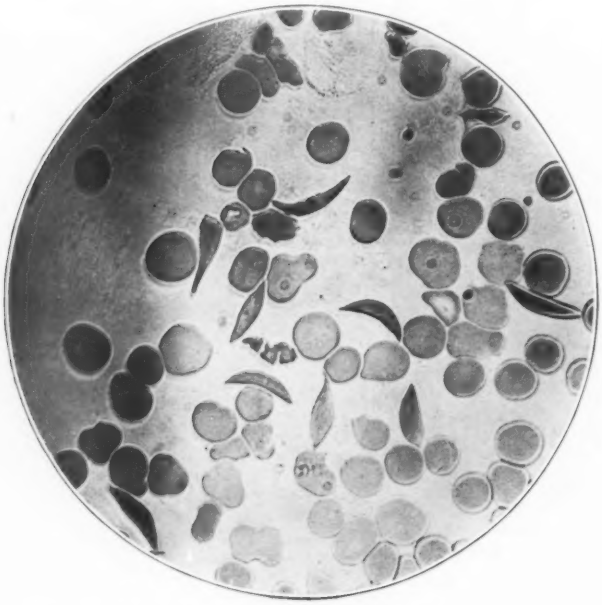

Fig. 10 (Case 2, R. R.).—Fresh blood preparation.

red or white cell counts, and the differential count showed no marked variations. Malaria and intestinal parasites were searched for daily, with negative results. Roentgen-ray examination of the chest revealed some general diffuse haziness of the lung shadows. The heart was described as much enlarged, mainly from left ventricular hypertrophy. The Pirquet test and the intradermal tuberculin tests were negative on two occasions. Splenic puncture was not attempted owing to objections by the family. The patient was discharged, clinically unimproved, on the demand of his family.

EXPERIMENTS WITH THE BLOOD OF THE TWO PATIENTS REPORTED AND THE BLOOD OF VARIOUS MEMBERS OF THEIR FAMILIES

An effort was made to confirm the observations of Emmel on the behavior of the fresh blood in sickle cell anemia. Parallel series of experiments were carried out on the blood of our two patients. As they were identical in all respects, the following descriptions apply to both.

Fresh coverslip preparations made on carefully cleaned glassware and sealed with hard paraffin showed rapid conversion of the circular erythrocytes into sickle forms. The sickle cells became more tenuous. This change began almost immediately, and, at room temperature, progressed until, at the end of twenty-four hours, almost all the erythrocytes had become deformed. This was not an apparent change due to hemolysis of the circular cells. Many of the shapes assumed were most bizarre, with long filamentous projections from the tips of the crescent shapes and various points on the concave margin of the sickles. The cells became darker and more "brassy" as though there were concentra-

Fig. 11 (Case 1, C. C.).—Fresh blood preparation, showing "sickling" after five hours.

tion of the hemoglobin. These cells were very plastic and could be distorted by pressure on the coverslip, but always returned to the original shape when the pressure was removed. Crenation sometimes occurred, but was strikingly abnormal, each little excresence being prolonged into a filamentous projection. Phagocytosis went on very actively in these sealed preparations. The large mononuclear leukocytes were apparently the only type of white cell exhibiting phagocytic activity.

Washed cells from the patients, mixed with centrifuged compatible serum from normal individuals, underwent the same changes at practically the same rate of speed as in the patient's own serum. This experiment was repeated with serums from patients suffering from a variety of diseases. Bile or bile pigments in the serums definitely

accelerated the sickling. This was noted both in serums from patients with biliary obstruction and in those with which minute amounts of bile had been mixed. Sodium glycocholate in extremely high dilution also accelerated the changes. Inactivated serums had practically the same effect as unheated ones, no definite difference in the time necessary to produce maximal sickling being noted. Serum is essential to the change, however. The patients' cells, suspended in 0.85 per cent. sodium chlorid, Locke's solution and isotonic glucose solutions, underwent no changes even after the lapse of a week. In these mediums, normal crenation frequently occurred after forty-eight hours.

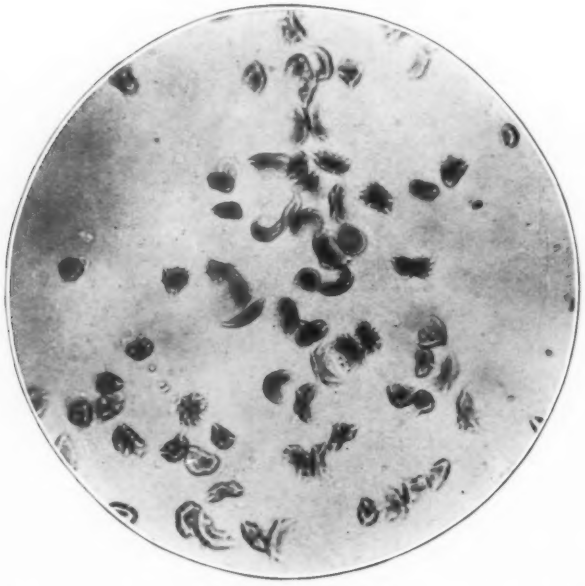

Fig. 12 (Case 1, W. C. [father]).—Fresh blood preparation, showing sickling after twelve hours.

Efforts to produce sickling in compatible cells of other individuals by mixing them with the patients' serums were without success. This experiment was performed with the cells of twenty individuals in each case, and nothing suggesting sickling was seen.

It was found that cold definitely inhibited the change. Preparations of the patients' blood placed in the icebox could be kept until hemolysis began without any increase in the number of sickle cells present. Heat, on the contrary, speeded up the process very definitely. Preparations kept in the incubator showed maximal sickling at the end of four hours.

Considerable interest was aroused by the active phagocytosis which was noted in the fresh preparations. Experiments were carried out

in an effort to produce similar phagocytosis of normal erythrocytes by the patients' leukocytes. Washed leukocytes from the patients were mixed with washed compatible erythrocytes in the patients' serums and in normal compatible serums. No phagocytosis was observed. Also, washed normal leukocytes from compatible blood were mixed with the patients erythrocytes in their own and in normal serums, and no phagocytosis took place.

Following the suggestion of Emmel and of Guthrie and Huck, the blood specimens of all the available members of the patient's families were examined. In addition, note was taken of the color of the sclerae,

Fig. 13 (Case 1, J. C.).—Fresh blood preparation, showing sickle cells immediately after making preparation.

the condition of the superficial lymph glands and the size of the spleen. These results are presented in Tables 2 and 3.

In Case 1, eight members of the family were examined. The paternal grandfather, C. C., aged 65, showed marked general glandular enlargement and greenish yellow sclerae. The spleen was not palpable. The blood showed no anemia and the fresh blood showed no sickle cells. After four hours, there was marked sickling, which became almost complete in twenty-four hours (Fig. 11). The father, W. C., aged 34, had yellow sclerae and marked general glandular enlargement. The spleen was not felt. The blood showed no abnormality in smears. The fresh preparations showed the typical sickle deformity in eighteen hours

(Fig. 12). The paternal uncle, T. C., aged 40, had white sclerae, but no general glandular enlargement and no splenomegaly. His blood was normal in all respects. The mother, M. C., aged 32, showed nothing abnormal in either physical or blood examination. The oldest brother, W. C., aged 11, had greenish sclerae and general glandular enlargement, but no splenomegaly. The blood showed a moderate secondary anemia

TABLE 2.—*Blood Findings in Family of Case 1*

	C. C. (Grandfather)	W. C. (Father)	W. C. (Brother)	J. C. (Brother)	A. C. (Patient)	R. C. (Brother)
Erythrocytes	4,312,000	5,240,000	3,560,000	2,056,000	1,328 000	3,662,000
Hemoblobin	75%	74%	70%	34%	25%	68%
Leukocytes	6,700	7,360	7,600	16,900	64 000	8,240
Sickle cells	4 hours	6 hours	4 hours	35%	20%	11%
Reticulocytes	.....	.....	.....	18%	15.4%	.....
Nucleated erythrocytes	None	None	None	Many	Many	Few
Neutrophils	46.4%	51.6%	35.6%	52.33%	78.1%	28.0%
Eosinophils	8.8%	4.8%	16 0%	3.00%	0.9%	3.0%
Basophils	2.4%	0.4%	0.0	0.66%	0.1%	0.0
Large mononuclears	8.0%	12 2%	8.0%	8.33%	2.6%	12.0%
Small mononuclears	30.4%	2. 2%	24.0%	29 66%	13.5%	50.0%
Transitionals	2.4%	2.0%	2.4%	2.33%	1.9%	6.0%
Large lymphocytes	0	0	2.4%	1.33%	0.9%	1.0%
Myelocytes	0	0	0	2.33%	0.8%	0
Unidentified	0	0	0.8%	0.33%	0.7%	0
Sclerae	Greenish	Greenish	Greenish	Greenish	Greenish	Greenish
Glands	Generally enlarged	Generally enlarged	Generally enlarged	Generally enlarged	Generally enlarged	Generally enlarged

TABLE 3.—*Blood Findings in Family of Case 2*

	J. R. (Father)	M. R. (Mother)	A. R. (Sister)	N. R. (Sister)	R. R. (Patient)
Erythrocytes	4,400,000	4,160,000	4,240,000	4,160,000	1,544,000
Hemoglobin	88%	80%	80%	80%	38%
Leukocytes	10,200	6,800	14,600	8,800	20,000
Sickle cells	12-16 hours	12-16 hours	2%	4 hours	27%
Reticulocytes	.....	.....	.....	.....	34%
Nucleated erythrocytes	None	None	None	None	Many
Neutrophils	46.8%	44.8%	36.4%	47.0%	33.0%
Eosinophils	2.4%	0.4%	2.4%	3.0%	2.2%
Basophils	0.0	0.0	0.0	1.0%	0.6%
Large mononuclears	15.6%	9.3%	22.0%	8.0%	9.0%
Small mononuclears	31.6%	42.8%	33.6%	37.0%	48.6%
Transitionals	3.6%	2.4%	5.6%	3.0%	4 8%
Myelocytes	0	0	0	0	0 8%
Unidentified	0	0.4%	0	0	0.6%
Sclerae	Greenish yellow	Slightly yellow	Greenish yellow	Greenish yellow	Dark green ish yellow
Glands	Generally enlarged	Slight enlargement	Slight enlargement	Slight enlargement	Generally enlarged
Spleen	Not palpable	Not palpable	Not palpable	Not palpable	Greatly enlarged

with marked poikilocytosis. The fresh preparations showed marked sickling in four hours. The second brother, J. C., aged 8, had dyspnea on exertion and intermittent attacks of "colic," and was weak and indolent. He had deep greenish-yellow sclerae and general glandular enlargement, but no splenomegaly. His blood showed a marked anemia, with a more striking picture of sickle-cell anemia than that of his brother A. C. (Fig. 13). The third brother, R. C., aged 23 months

had greenish yellow sclerae and general glandular enlargement, but no splenomegaly. He was well. The blood showed a moderate anemia, with many sickle cells in the smears and fresh preparations. The sister, L. C., aged 10 months, was normal in all respects.

In Case 2, only four members of the family would submit to examination. These were the father and mother and two sisters, aged 13 and 11. Both the father and mother had greenish yellow sclerae; the father had marked glandular enlargement, and neither had a palpable spleen. Both had normal blood counts and smears, but both had active sickling in the fresh blood after twelve hours. (Figs. 14 and 15.) Both sisters

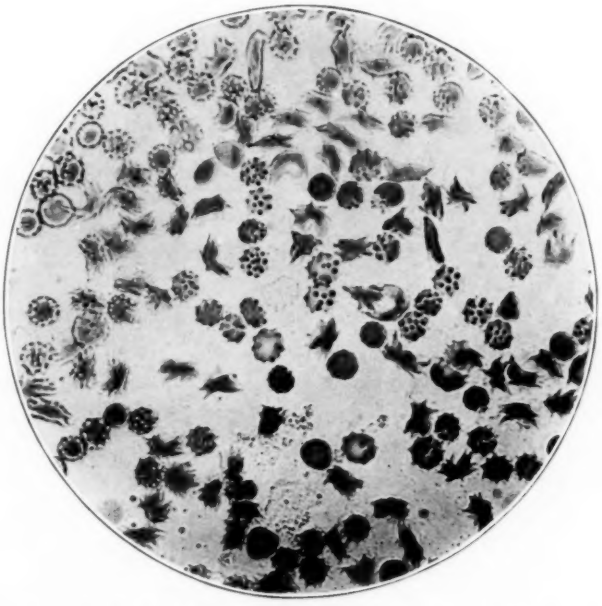

Fig. 14 (Case 2, J. R.).—Fresh blood preparation, showing sickling and crenation after eight hours.

had yellow sclerae and general glandular enlargement, with no splenic enlargement. Both had normal blood counts with the exception of a slight eosinophilia. The older sister had a few typical sickle cells in her smears (about 2 per cent.) and showed maximal sickling in six hours (Fig. 16.) The second sister had normal appearing fresh blood, but it showed maximal sickling in eighteen hours.

COMMENT

The chief interest in the two cases reported lies in the necropsy findings in Case 1, and the presence, transient though it was, of nucleated sickle cells in the blood in Case 2. Previous observers, in the absence

of pathologic examination of the cases and of any etiologic agent that could be discovered, have been inclined to ascribe the peculiar poikilocytosis present in this condition to changes that took place in the blood after the cells reached the peripheral circulation. The changes present in the bone marrow in Case 1 are unlike any that we found recorded. The presence in the marrow of sickle shaped, filiform and otherwise abnormal erythroblasts, with erythrocytes to correspond to these various types, seems to warrant the conclusions that the sickle cells seen in the peripheral blood are not the result of changes that go on in the circulation or in the splenic sinuses but that they are per-

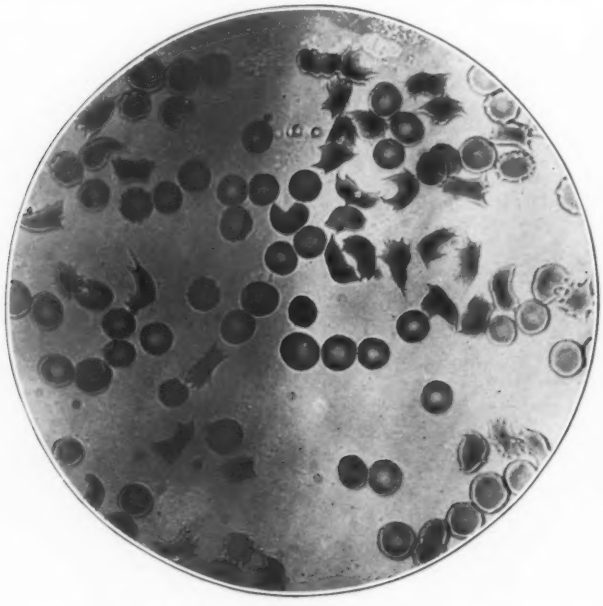

Fig. 15 (Case 2, M. R.).—Fresh blood preparation, showing sickling after eight hours.

formed in the marrow as the result of some primary fault of erythropoiesis, the cause of which is as yet unknown. The presence of nucleated sickle cells in the blood in Case 2 adds some confirmation of this view.

Both our patients had attacks of high abdominal pain, localized in the epigastrium and left hypochondrium. In three of the reported cases, those of Herrick, Washburn and Mason, there were similar attacks. We lay stress on this symptom in view of the unusual findings in the spleen in Case 1. It was evident that there had been repeated hemorrhages into the spleen, and the spleen itself was greatly reduced in size. In all the reported cases, it was specifically mentioned that the spleen

was not demonstrable clinically. It seems possible that the epigastric pain and perhaps the gastric disturbances were due to splenic hemorrhages.

In all the reported cases, in our cases and in the members of the families of our patients who showed "latent sickling," a peculiar scleral discoloration was present. This was not frank jaundice, but a greenish yellow pigmentation much like that seen in familial hemolytic icterus. The urine in Herrick's case showed a trace of bile; in Mason's also bile was found. Washburn's case showed bile in the urine. No mention is made of the examination in Cook and Myer's case. Both of our

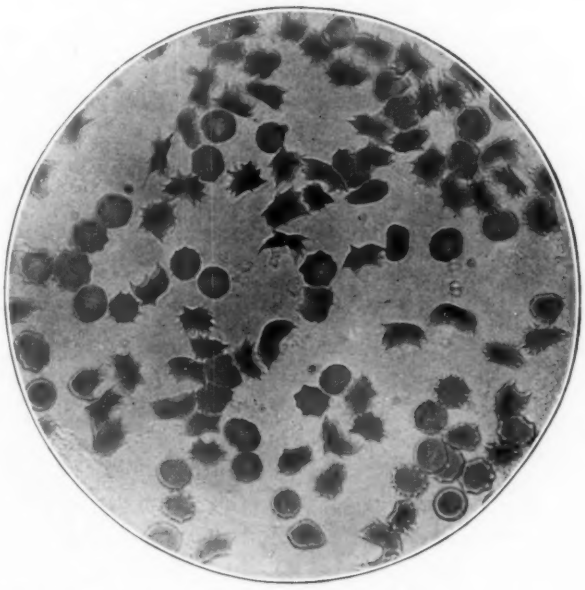

Fig. 16 (Case 2, A. R.).—Fresh blood preparation, showing sickling after four hours.

cases showed a heavy urobilinuria and a bright yellow serum suggesting urobilinemia. In the liver and kidneys in Case 1, there were many brown granules, in the Kuppfer cells of the liver and in the epithelium of the kidney tubules. These findings suggest most strongly that there is a hemolytic factor in the production of the anemia. Whether hemolysis is initiated by some element inherent in the blood of these individuals or whether it is dependant on extraneous factors, we are unable to state. The phagocytosis of erythrocytes in the circulating blood noted by Emmel and occurring in both our patients may have some bearing on this phase of the condition. In this connection, it may be mentioned that, in the blood of all the members of these two families who showed

"latent sickling," there was active phagocytosis in the sealed preparations though none was noted in the stained smears of their blood.

The changes observed in the blood of the grandfather, father and oldest brother in Case 1, and in all the relatives in Case 2 who were examined, were identical with those described by Emmel in the father in the case he studied. They are also identical with the changes which go on in the blood of individuals with frank sickle cell anemia. Emmel's patient passed through a period during which her blood returned to normal so far as could be determined from stained smears, but when it was allowed to stand for four hours, many of the cells assumed the characteristic appearance found on previous examinations. We have termed this phenomenon "latent sickling," and feel that it has the same significance as the occurrence of sickle cells in the freshly smeared blood, the difference being one of degree and probably dependant on extraneous factors.

The blood of more than 300 white patients has been examined by us with special reference to "latent sickling," and in no case has anything resembling it been seen. In a similar number of negroes, it was found thirteen times, exclusive of its occurrence in the families in the cases reported. This adds weight to Mason's hypothesis that sickle cell anemia is a condition peculiar to the negro race.

SUMMARY

1. Two cases of sickle cell anemia occurring in negro children are reported.

2. Necropsy in one case revealed hitherto undescribed changes in the bone marrow which suggest that the changes in the blood are dependant on a primary defect of blood formation.

3. There is evidence that there is active hemolysis of erythrocytes in addition to disturbances in erythropoiesis.

4. Several members of the patient's family in each case showed changes in the blood analogous to those presented by the patient.

5. No similar changes in the blood of white persons has been described.

CONCLUSION

We feel warranted in stating that sickle cell anemia is a definite clinical entity, characterized by a definite symptom-complex and by specific blood findings and anatomic changes, and that it is a familial disease. There is strong evidence that it occurs only in the negro race or in persons of mixed blood.

RICKETS IN AN INFANT OF THIRTY-FOUR DAYS *

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The earliest age at which rickets begins and the precise time required for the development of the pathologic process in the bones are not definitely known. Craniotabes, the first clinical sign of involvement of the skeleton, has been described in the second month; ordinarily, however, it does not manifest itself before the third or fourth month. By the fourth month, the enlargements at the lower ends of the radius and ulna and at the costochondral junctions may have attained such size as to be recognizable on physical examinaiton, but then the rachitic process is already advanced. Craniotabes makes its appearance at a time when the pathologic process at the ends of the ribs and long bones of the extremities is in an early stage of development, and it is the earliest positive sign of rickets.

The difficulty in regard to the value of craniotabes in the diagnosis of rickets lies in the fact that defective calcification of the skull occurs in conditions other than rickets. When, however, craniotabes develops while an infant is under observation, or is widespread in the region of the lambdoidal suture, it alone justifies the diagnosis of rickets. One who relies on enlargements of the costochondral junctions for the diagnosis of early rickets will often fail to recognize the disease when present, and will believe it present when it does not exist.

Though rickets can be diagnosed by means of the roentgen ray earlier than by physical examination, it cannot be recognized by the roentgen ray at the earliest stages of its development in the bones.

The laboratory offers the means of earliest diagnosis. Rickets, as is now well known, is characterized by a disturbance in the salt equilibrium of the body. The investigations of Howland and Marriott,[1] Kramer, Tisdall and Howland,[2] which have been confirmed by numerous others, have shown that, in infantile tetany (in reality rickets accompanied or complicated by tetany), there is a diminution of the calcium in the blood serum; and investigations of Iversen and Lenstrup,[3] Howland and Kramer [4] and others have shown that, in rickets

* Received for publication, June 12, 1923.

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1. Howland, J., and Marriott, W. McK.: Observations Upon the Calcium Content of the Blood in Infantile Tetany and Upon the Effect of Treatment by Calcium, Quart. J. Med. **11**:289, 1917-1918.

2. Kramer, Benjamin; Tisdall, F. F., and Howland, John: Observations on Infantile Tetany, Am. J. Dis. Child. **22**:431 (Nov.) 1921.

3. Iversen, P., and Lenstrup, E.: Calcium and Phosphorus in the Serum in Relation to Rickets, Forhandlingerne ved Forste Nordiske Kongres for Paediatri, 1920; cited by Howland and Kramer.

4. Howland, John, and Kramer, Benjamin: Calcium and Phosphorus in the Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

unaccompanied by tetany, a diminution in the inorganic phosphorus of the blood serum is characteristic. In rickets, therefore, there may be a decrease in the calcium of the blood serum or in the inorganic phosphorus, or in both. Although information of an absolute nature is lacking, it seems probable that the changes in the salt equilibrium of the blood just mentioned precede the development of recognizable pathologic changes in the bones.

The question as to the occurrence of congenital rickets is still debated. At present, one can say merely that no reliable evidence of the occurrence of congenital rickets has ever been produced. Convincing demonstrations of rickets in the bones of new-born children have never been made. Schmorl [5] searched for rickets in the bones of 100 new-born infants, both full term and premature, but failed to find evidence of the disease in a single instance. It is probable that congenital rickets occurs rarely, if at all. There can be no doubt, however, that at birth certain children are more predisposed to the development of rickets than others. For example, premature infants and twins are more liable to develop rickets than infants born at term and born singly, and the offspring of certain families or races appear to be especially susceptible to influences which are factors in the production of rickets.

The reason for the peculiar susceptibility of the premature infant to rickets has never been explained. Hamilton [6] has recently found evidence to show that, under normal conditions, during the last three months of intra-uterine life, the fetus stores calcium in the skeleton, and, during the first few months of extra-uterine life, the normal infant draws on the store of calcium. However, he did not obtain evidence of a corresponding formation of a phosphorus depot in the last months of fetal life or a subsequent dependence on a phosphorus depot. He suggests that the peculiar susceptibility of the premature infant is due to a deficiency of stored calcium in the skeleton. The susceptibility of the premature infant to rickets may arise from the condition of immaturity of the organism and from the demands resulting from the great growth stimulus. The premature infant is not only more susceptible to rickets than the child born at term but also develops the disease at an earlier age.

The occurrence of rickets at a very early age has been reported by Schmorl,[5] Hamilton [6] and Ylppö.[7] Schmorl found rickets at

5. Schmorl, G.: Die pathologische Anatomie der rachitischen Knochenerkrankung mit besonderer Berücksichtigung ihrer Histologie und Pathogenese, Ergebn. d. inn. Med. u. Kinderh. **4**:403, 1909.

6. Hamilton, B.: The Calcium and Phosphorus Metabolism of Prematurely Born Infants, Acta Paediat. **2**:1, 1922.

7. Ylppö, A.: Zur Physiologie, Klinik und zum Schicksal der Fruhgeborenen, Ztschr. f. Kinderh. **24**:1, 1920.

necropsy at one and one-half months. Apparently, no clinical evidences of the disease were present. Hamilton observed the development of rickets, as evidenced by craniotabes, in two premature infants during the sixth week of life. Ylppö reported rickets in a premature infant aged one and one-half months.

The case of rickets here reported is of unusual interest on account of the advanced stage which the disease had attained at an extremely early age.

REPORT OF CASE

History.—M. G., an Italian, born June 11, 1922, was admitted to the New Haven Hospital, July 15, at the age of 34 days. The father was well. The mother, who was 34 years old, had marked scoliosis and developed a "weakness of the extremities" and pains in the legs which forced her to remain in bed during the last three months of pregnancy. A roentgenogram of her spine (Fig. 5), taken on admission to the lying-in hospital, revealed a marked degree of scoliosis and rarefaction of the verebral column, humerous and ribs. Though a diagnosis of osteomalacia could not be made from the roentgenogram alone, it seems altogether probable that the mother was suffering from osteomalacia at the time the infant was born. There had been seven previous pregnancies, and all the children were living and well.

The diet of the mother, until about one month before the birth of the child, was most defective, consisting chiefly of milk, potatoes, macaroni and bread. The value of this diet per day was estimated to be about 1,846 calories: the calcium, per hundred grams of food, 0.6 gm.; the phosphorus, 1.2 gm. (average normal, calories, 3,000; calcium, 0.45 gm.; phosphorus, 0.88 gm.). The mother spent the last month of pregnancy in the hospital and ate the ordinary hospital fare.

The home conditions were poor. The family, consisting of eight persons, occupied three rooms on the first floor of a dark and dirty brick tenement. One bedroom had two windows on the east, another two windows on the north side. The kitchen also had two windows on the north side. The northern exposure, however, was not of great value because the light was cut off by a high building close by. The house was extremely dirty, dark and damp.

According to the mother's calculation, the patient was born two months prematurely. The birth weight of 3,260 grams (recorded at hospital) indicates that the child was born at term. No abnormalities were noted at birth. It is believed that the baby was breast fed for a few days, then given a supplementary formula. Later, it was fed entirely on a formula which was a mixture of whole milk, water and sugar, the exact composition being unknown.

Examination.—On admission to the New Haven Hospital (at the age 34 days), the infant was small and poorly nourished. The circumference of the head was 36 cm.; chest, 32.2 cm.; abdomen, 32.5 cm.; length, 50.5 cm.; weight, 2,600 grams. The head showed extensive craniotabes, involving symmetrically almost all of the upper and posterior part of the parietal bones and the anterior portion of the occipital bones. There was slight but definite enlargement of the epiphyses of the wrists. The lungs were clear. A loud blowing systolic murmur (due to a patent intraventricular septum) was heard over the whole precordium, and was transmitted to the axilla and back. The spleen was felt. There was no evidence of infection. The diagnosis was: rickets, and congenital malformation of the heart.

The roentgenograms of the radius, ulna, tibia and fibula taken, July 17, when the baby was only 34 days old, revealed marked rickets (Fig. 1). The lower ends of both radius and ulna were abnormally broad and cupped. They did not end sharply, but had a frayed appearance. The shafts cast a less dense shadow than that caused by normally calcified bone. The tibia and fibula showed

similar changes. At that time, the calcium of the blood was 9.0 mg. per hundred cubic centimeters of serum; the inorganic phosphorus, 2.2 mg. per hundred cubic centimeters of serum. There was a moderate secondary anemia, with hemoglobin 50 per cent. and 4,408,000 red blood cells. The blood Wassermann reaction was negative. The tuberculin test (0.02 mg., intradermally) was negative. The urine examination was negative.

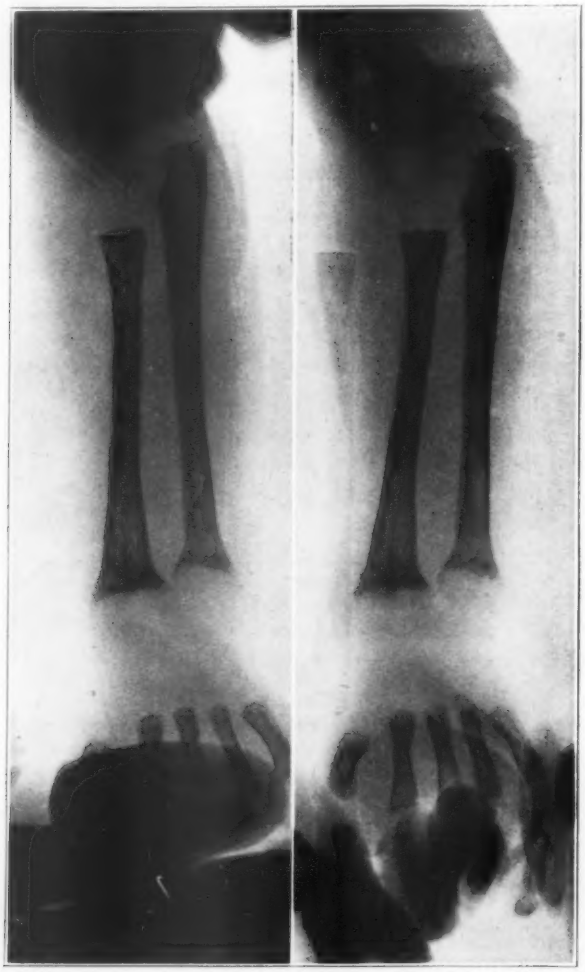

Fig. 1.—Radius and ulna. The flaring of the lower ends of the bones, the irregular frayed appearance, lack of calcium deposition and rarified appearance of the bone are evident.

Outcome.—The baby did not thrive. August 14, the temperature rose abruptly, and signs of pneumonia developed. August 15, at the age of 2 months, the infant died.

Necropsy Findings.—Rickets, congenital malformation of the heart and terminal bronchopneumonia were found. The thorax showed typical deformities.

The costochondral junctions were greatly enlarged on the inner surfaces and were slightly enlarged externally. Twenty-four fractures of the ribs were counted, and doubtless many more were actually present (Fig. 2). They were green-stick fractures and were marked by callus formations which formed distinct enlargements on the inner surface of the thorax. The ends of the radius and ulna and tibia and fibula showed characteristic enlargements. The bones offered little resistance to cutting. The slices taken longitudinally through the the cartilage-shaft junctions showed the typical rachitic intermediate zone or metaphysis.

Histologic Examination.—On microscopic examination of the lower end of the radius (Figs. 3 and 4), the proliferative zone of cartilage was considerably

Fig. 2.—Low power view (magnification × 9) of the lower end of the radius of M. G., at age of 2 months. The irregularity of the junction of the cartilage with the shaft is characterized by an intermingling of prolongations from the cartilage (*k*) and prolongations from the shaft (*b*). Depositions of lime salts can be seen near the terminations of some of the prolongations of the cartilage (*l*). The proliferative zone of cartilage is much wider than normal. The trabeculae (*c*) are readily seen, and the osteoid borders easily recognizable. The marrow (*d*) seems fairly normal. The marrow does not fill in all the interspaces between the trabeculae. The trabeculae are surrounded by investments of fibrous tissue, which for the most part exclude the marrow from the spaces between them.

deeper than normal and sent numerous irregularly shaped prolongations toward the shaft. The cartilage cells composing the prolongations were for the most part in the same stage of development as those found normally in the proliferative zone close to the shaft. At the borders of the prolongations, however, in close proximity to the blood vessels of the marrow, the cells had lost their staining properties, and they and their matrix were undergoing transformation into osteoid.

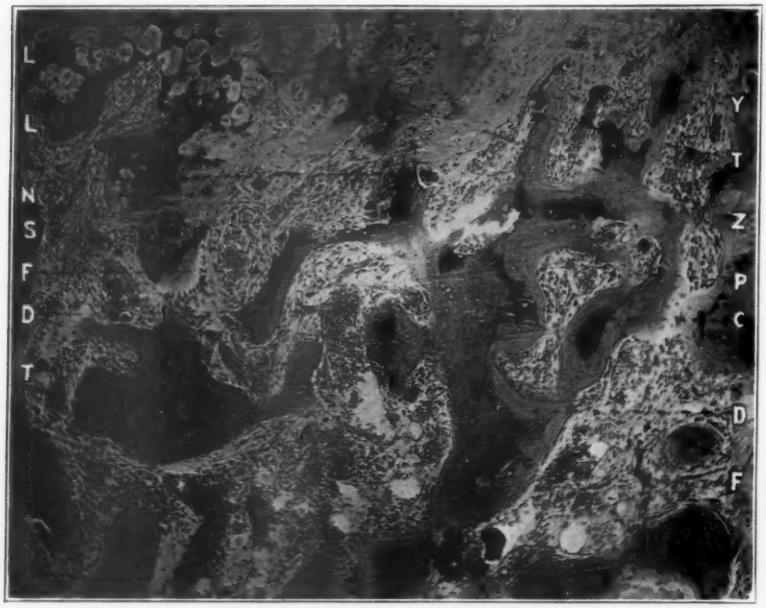

Fig. 3.—High power view (magnification ×70) of the lower end of the radius. At *z* can be seen the end of one of the prolongations of cartilage extending from the proliferative zone to the shaft through the rachitic metaphysis or transitional zone. The peripheral portion of this prolongation of cartilage has lost its normal staining reaction to hematoxylin and is undergoing transformation into osteoid (*y*). The cartilage cells are taking on the characteristics of osteoblasts. At *l* can be seen dense deposits of lime salts, appearing as irregular black areas. The characteristic changes in the trabeculae are well shown. In their central portions, the trabeculae are calcified, but in the peripheral portions they are free from lime salt deposits, and appear light pink in the preparations stained with eosin and hematoxylin. The trabeculae present, therefore, the osteoid borders characteristic of rickets. In the osteoid, the bone corpuscles can be plainly seen. The investments of fibrous tissue (*f*) about the trabeculae are also visible. The fibrous tissue lies next the trabeculae, and separates the marrow (*d*) from the trabeculae. The destruction of the trabeculae is proceeding apace. At *p*, the calcified central portion of the trabecula is being destroyed. In many parts of the sections, there seems to be a selective destruction of the calcified portions of the trabeculae rather than of the uncalcified portions by the blood vessels with their investments of cells (the perforating canals of the German pathologists). At *t*. the osteoid borders of the trabeculae have been destroyed, and the central cores have been exposed, eroded and in large part destroyed. The same has occurred at *s*. Where destruction of the lateral portions of the trabeculae is taking place, osteoclasts (*n*) are numerous. Osteoclasts also are found in niches or cavities at the edges of the trabeculae. In general, the osteoclasts lie against or close to a calcified portion of the trabecula, but some of them seem to lie in contact with the uncalcified portions. The evidences of the destruction of the trabeculae are almost as marked in the bones of M. G. as in the bones of rachitic rats on diets deficient in calcium.

At certain points, particularly where pressure was being exerted, the cartilage cells seemed to be reverting to earlier stages of development. At the ends of some of the prolongations were heavy deposits of lime salts. The prolongations of cartilage were separated from each other by prolongations in the opposite direction from the marrow. The latter were composed of blood vessels, some of which terminated close to the cartilage cells in bulbous enlargements. An enveloping loose connective tissue was also present. This connective

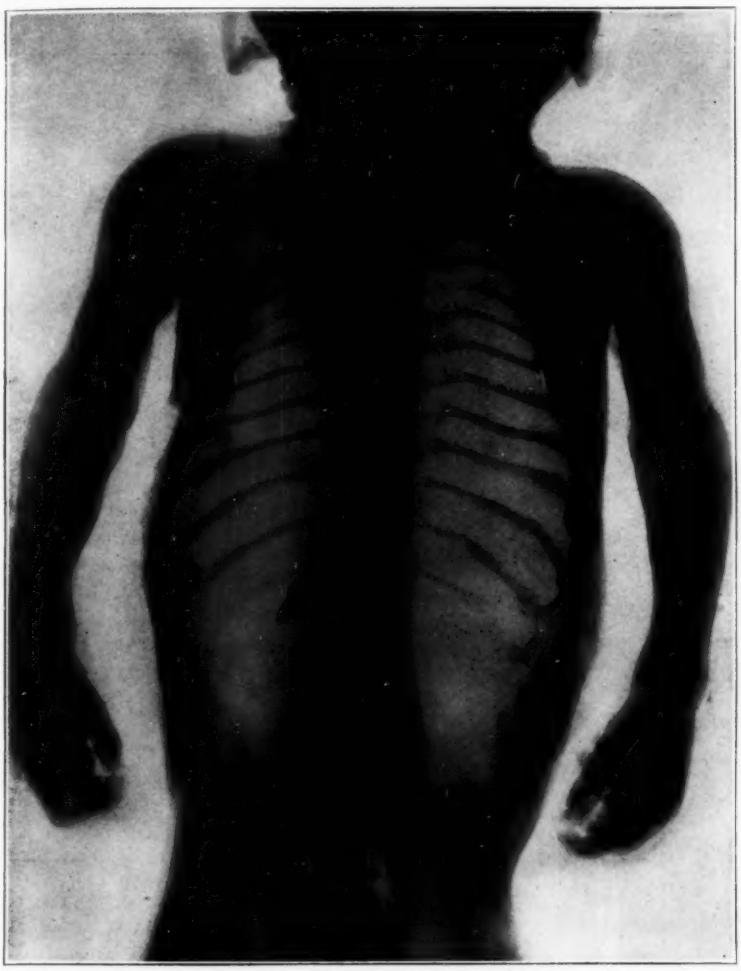

Fig. 4.—Thorax and upper extremities of patient after viscera had been removed. Numerous fractures of the ribs and marked flaring of lower ends of long bones, with cupping, are evident; also the absence of normal density in the cartilaginous zone.

tissue had a gray appearance in the hematoxylin and eosin stained specimens, and consisted of long thin connective tissue cells having rod-shaped nuclei (the "fibrous marrow" of the German authors). The prolongations from the marrow, interdigitating with the prolongation from the cartilage, together formed the rachitic metaphysis.

At different points in the metaphysis, there were small masses of cartilage cells which, in the sections, seemed to be completely cut off from the main mass of cartilage. These were undergoing change into osteoid. The trabeculae of bone were calcified centrally. Their margins, however, were free from lime salt deposition, and formed the typical osteoid borders which are characteristic of rickets. The trabeculae were surrounded by thick investments of the connective tissue already described. Evidences of the destruction of trabeculae were found everywhere.

Fig. 5.—Thorax of Mrs. G., mother of patient. The roentgenogram reveals marked scoliosis and rarefaction of clavicles and scapulae. It is not sufficiently good to permit positive diagnosis of osteomalacia, but strongly suggests that condition.

In some places, blood vessels surrounded by investments of cells seemed to have bored into the calcified and also the uncalcified portions of the trabeculae, destroying them. In other places, the osteoid sides of the trabeculae had been destroyed, and the calcified portions were exposed and evidently undergoing erosion. In such places, osteoclasts were invariably found. Osteoclasts, whatever their function, were exceedingly numerous at the margins of the trabeculae. They either lay along the eroded sides or in holes or small hollows at the sides or tips.

COMMENT

This case, then, was one in which rickets was already well developed at the age of 34 days. Craniotabes was so marked that from it alone the diagnosis could be made. Roentgenograms of the wrists and ankles revealed indisputable evidences of advanced rickets. The blood at that time showed a normal calcium, but a low inorganic phosphorus. It is thought that 34 days is the earliest age at which rickets has ever been proved to be present.

MALIGNANT EPITHELIAL THYMOMA

REPORT OF A CASE, WITH NECROPSY *

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AND
HELEN HARRINGTON, M.D.
CINCINNATI

Cases of malignant thymoma are rare. Rubaschow [1] compiled a list of thymic tumors described prior to 1911, including a series collected by Hoffman in 1896, which totaled fifty-two sarcomas, twelve carcinomas and ten tumors of various other types. Since then, barely a dozen had been reported, when one of us (Foot [2]) described a case in 1920; and only four reports are subsequently listed in the *Quarterly Cumulative Index* of the American Medical Association to date.

As the histology of malignant thymoma was presented and discussed fully in the 1920 article just referred to,[2] we shall limit ourselves to a summary of Ewing's excellent article on these tumors in his textbook on neoplastic diseases,[3] and to a brief review of an article by Symmers and Vance,[4] which has an important bearing on our case.

MALIGNANT NEOPLASMS OF THE THYMUS

There are three types of malignant neoplasm of the thymus: (1) lymphosarcoma; (2) carcinoma, and (3) spindle cell or myxosarcoma, which is very rare and whose exact origin is undetermined. Ewing believes it to be the same as that of the other types, the thymic reticulum.

1. Lymphosarcomas occur in the anterior mediastinum in young persons, surrounding and compressing the trachea, bronchi, pericardium and great vessels. They cause death by compression asphyxia and venous obstruction, which may come on gradually or suddenly. The more rapidly growing tumors are soft; but, as a rule, thymomas show a firm, nodular consistence, owing to fibrosis. The soft tumors may be very vascular and hemorrhagic. Rarely, one encounters cyst formation or softening. They may exhibit a lemon or creamy yellow

* Received for publication, June 12, 1923.

1. Rubaschow, S.: Virchows Arch. f. path. Anat. **206**:141, 1911.

2. Foot, N. C.: Report of Case of Malignant Thymoma with Necropsy, Am. J. Dis. Child. **20**:1 (July) 1920.

3. Ewing, James: Neoplastic Diseases, Ed. 2, Philadelphia, W. B. Saunders Co., 1922, pp. 912-923.

4. Symmers, Douglas, and Vance, B. M.: Epitheliomas of Thymic Origin, Arch. Int. Med. **28**:239 (Sept.) 1921.

color. A strict encapsulation within the mediastinum has been a notable feature, but the more malignant tumors regularly adhere to the surrounding organs. The bronchial, cervical and axillary nodes have been invaded occasionally; but direct extension into the pleura and pericardium is rather characteristic, the hilum of the lung often remaining comparatively free. While most of these tumors are rather sharply limited to the thorax, metastasis to distant organs, such as the spleen, liver, pancreas, suprarenals, and kidneys have been observed. Perforation of the chest wall may take place.

The microscopic structure varies. In one group, it resembles that of Hodgkin's granuloma. Large cells appear and displace the lymphocytes, giving rise to a picture that resembles that of carcinoma. Sometimes, the tumors may be composed exclusively of small cells, but "the existence of a pure lymphocytoma of the thymus, apart from leukemia, does not seem to have been established." Ewing believes that the tumor cells are not lymphocytes, for they differ materially from these in their structure. Lymphocytes are scanty. The chief cell showing active growth and mitosis is often polyhedral, with an acidophil cytoplasm, vesicular nucleus and well-developed nucleoli. Abortive Hassal's corpuscles may be produced.

2. Thymic carcinoma occurs in elderly persons; shows less tendency to metastasize than do most carcinomas, and is composed of sheets or columns of large, flat or polyhedral cells, with a dense connective tissue stroma. No cornification takes place, but structures resembling Hassal's corpuscles may be found. Ewing believes that this type of thymoma may be connected in some way with a perversion of the involution of the gland. Our case, occurring in a child of 2 years, would indicate that this is not necessarily true.

3. Thymic sarcomas of a spindle cell type have been described, and their origin attributed to the stroma of the gland. Myxosarcomas in which myxomatous tissue contained lymphocytes and Hassal's corpuscles have been reported.

Ewing strongly inclines to the view that the thymomas may be of infectious origin, a theory analogous to that held by many in connection with Hodgkin's granuloma. Having reviewed the material of one of Symmer's cases, which is indistinguishable from a thymoma, he believes that many cases described as Hodgkin's granuloma of the mediastinum are, in reality, thymomas; and he thinks that the two processes may be of an inflammatory, rather than a neoplastic, origin. It would seem, however, that there is no better actual proof that this is so than there is that the contrary is true; both thymoma and Hodgkin's granuloma may be placed just as readily in the category of

neoplasms, with a brisk reaction on the part of the stroma and evidence of chronic inflammation due to the presence of tumor cells.

In reporting a case of epithelioma of thymic origin, Symmers and Vance [4] outline the types and groups of thymic tumors much as does Ewing, but they add that the term "thymoma," as applied to the lymphoid tumors, is permissible, if at all, only when used to denote a tumor that reproduces the structure of the thymus as a whole, including lymphocytes, epithelial reticulum cells and Hassal's bodies. They state that but four examples of true primary epithelioma of this organ are to be found in the literature, including theirs. One case each was reported by Paviot and Gerest,[5] Thiroloix and Debre,[6] and Rubaschow.[1] We shall return to a discussion of Symmers' and Vance's paper later, when comparing our case with theirs. In concluding, these authors state that the lymphocytic tumors are much more numerous than the epithelial and occur in persons under 35 years of age, many of them in children; while the four recorded cases of epithelial type have occurred in persons over 50.

REPORT OF CASE

History.—A girl, aged 2 years, colored, admitted to the Cincinnati General Hospital, March 5, 1923, having been brought in by her foster-mother, with whom she had lived for over a year and by whom the meager history was given, was thought to have enlarged tonsils, and this was the chief complaint. Her father and mother, who had six children, were alive and well, as were four of the children. The other child had died of a cause undetermined.

Prior to the time the patient came to live with her foster-mother, her history was unknown. She had never been well since coming under this woman's observation, having constant "trouble with her throat," difficulty in swallowing and paroxysms of coughing and strangling while attempting to drink, but apparently no pain. She would "pick at her throat," particularly at night, and her symptoms were subject to variations in intensity. She had no dyspnea, except when she had a paroxysm of coughing. She had fever at times, when the coughing was at its worst, and her foster-mother attributed it to tonsillitis. Although she frequently gagged, she did not vomit; her appetite was good, and she gained steadily on a diet of milk and potatoes, although she was very constipated. She had no important urinary symptoms.

Physical Examination.—At the time of admission, it was noted that respiration was slightly exaggerated, the alae nasi moving with each breath. The child was mentally alert and apparently not in pain, but she pulled constantly at her throat with her hands. The tonsils were very large, and the cervical, axillary and inguinal lymph nodes were palpable. No pharyngeal abnormality could be determined on digital examination. The patient was not cyanotic.

The chest was well developed. The lungs showed normal resonance throughout the right side, but resonance was impaired over the left apex anteriorly and posteriorly, and was higher-pitched over most of the left side of the chest. The breath sounds were close to the ear and harsh over the right chest, and somewhat prolonged over the apex. In the left side of the chest,

5. Paviot, J., and Gerest: Arch. de méd. expér. et d'anat. path. **8**:699, 1896.

6. Thiroloix, J., and Debre, R.: Arch. de méd. expér. et d'anat. path. **19**:668, 1907.

these sounds were somewhat suppressed throughout, but this condition was most marked at the apex, where prolonged expiration was best heard. There were a few râles in the left apex, but no adventitious sounds were heard elsewhere.

The right border of the heart was apparently normal, but the left was difficult to determine on account of the impaired resonance on that side of the thorax. The heart sounds were loud and clear at the apex and comparatively clear elsewhere. There was a loud systolic murmur heard everywhere over the left side, but most marked in the second interspace in the nipple line. The abdomen projected above the level of the thorax. There was no palpable rigidity or masses. The liver and spleen were not felt. The patient winced on deep palpation. The reflexes were all normal.

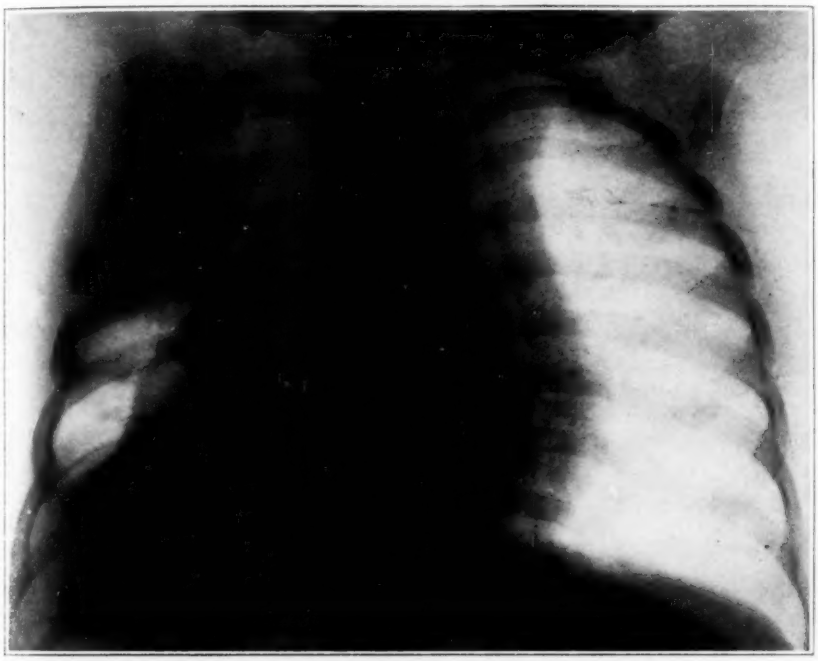

Fig. 1.—The striking similarity of the densest shadow on left to enlarged heart is evident (taken, March 10).

Summary: The principal findings on examination were: 1. Constant clutching at throat. 2. Large tonsils. 3. Impaired percussion note over left side of chest, with most marked impairment at apex. 4. Roughened voice sounds and diminished breath sounds over left side of chest. 5. Systolic cardiac murmur heard everywhere over left side of chest, but best in second left interspace.

Admission diagnoses: (1) Hypertrophic tonsils and (2) unresolved pneumonia in the left apex were diagnosed.

Course in Hospital.—March 6: The larynx was examined, but nothing abnormal was detected. Fluoroscopic examination of the esophagus after the ingestion of a barium sulphate meal failed to demonstrate anything of a pathologic nature.

March 10: Roentgenograms revealed a marked increase in all diameters of the heart, suggesting congenital enlargement. There was also a definite haziness over the left apex, suggesting infiltration. The fact that the diaphragmatic shadow was very high on the left pointed to some subdiaphragmatic pathologic condition (Fig. 1).

March 21: The patient's temperature rose to 102 F. and she coughed frequently. The chest signs were little changed.

March 28: Fluoroscopic examination revealed an area of density in the upper left lobe, extending almost to the base. The diaphragm was still high and fixed, being apparently held by adhesions. Two unsuccessful attempts were made to aspirate the left side of the chest.

Fig. 2.—Complete obliteration of left side of chest by large shadow is shown (taken, April 3).

March 29: She lost her appetite and had difficulty in swallowing. She suffered also from attacks of dyspnea. The percussion note was now markedly impaired over the entire left chest, except anteriorly at the base. The breath sounds were distant and tubular on this side, and harsh, with occasional coarse crackles or wheezes over the right.

March 31: Signs of fluid in the left chest, confirmed by roentgen ray, were so marked that aspiration was again carried out, about 50 c.c. of fluid being removed. This at first appeared to be pure blood, but on centrifugation showed but two parts of red cells to ten parts of fluid, and a lower red count than normal for blood. Stained smears showed no abnormal cells, and cultures were sterile. The presence of bloody fluid at this time was thought

to be the result of the trauma incidental to the first aspiration. No pathologic cells were found, such as might indicate the presence of a tumor.

April 9: The heart was displaced to the right; signs of fluid were still present, and aspiration resulted in the withdrawal of 50 c.c. of straw-colored fluid, in which no tumor cells were found.

April 21: Roentgenograms revealed the density already referred to persisting over the entire left chest. Plates taken between March 12 and April 21 showed merely a progressive increase in this density and in its extent (Fig. 2).

April 26: Signs of fluid in the left side of the chest again became more marked, and 125 c.c. of dark, bloody fluid was removed. It was now felt that the presence of blood could not be accounted for on the basis of trauma alone. The presence of a new growth, affecting the pleura, was considered probable,

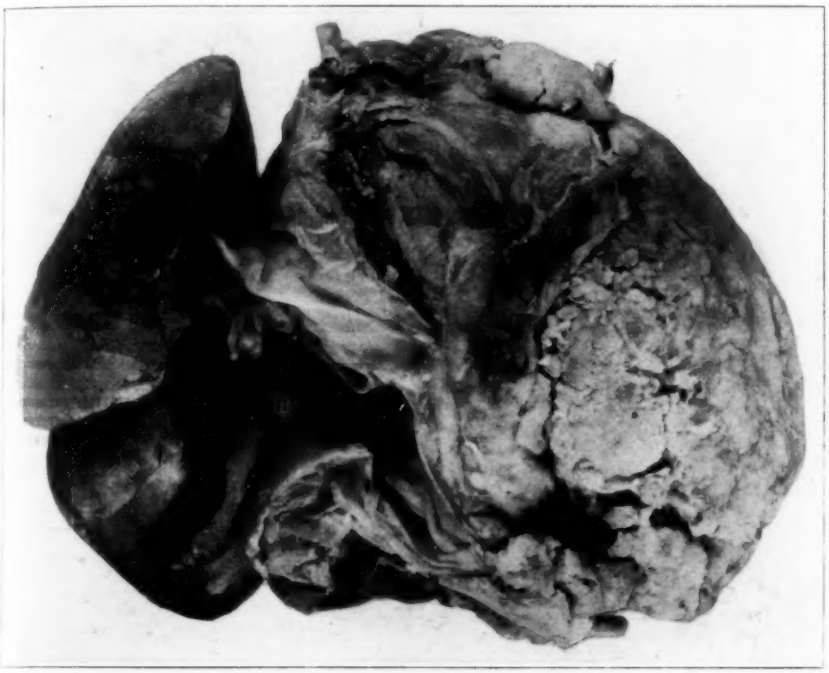

Fig. 3.—Anterior view of tumor and right lung. The heart has been removed from the dark recess at left center. The compressed thymus is visible at upper center to left of prominent nodule.

although roentgenographic examination revealed no masses, and no tumor cells had been found in the fluid previously. That obtained at this time was lost through accident and no examination could be made.

April 29: Aspiration was again attempted, with the hope of securing enough fluid for sections of a clot, but only 2 or 3 c.c. was obtained. Smears showed no abnormal cells and cultures were sterile. The patient gradually became weaker and more apathetic, the cough and dyspnea increasing

May 10: Respiration became very rapid, and the patient would lie only on the left side. No breath sound could be heard on the left and they became diminished on the right. The percussion note was hyperresonant over the right side, except at the base, where there was some impairment. The heart was rapid It was displaced to the right, and its sounds were very weak. In the evening, the child died suddenly of cardiac failure and pulmonary edema.

Laboratory Findings.—Urine examination, throat cultures, vaginal smears, tuberculin and Wassermann tests and all cultures from the pleural fluid were negative.

Blood examination (March 5) revealed: white blood count, 17,600; polymorphonuclears, 32 per cent.; eosinophils, 1 per cent.; lymphocytes, 65 per cent.; large mononuclears and transitionals, 2 per cent.; (March 30): white blood count, 14,600; polymorphonuclears, 61 per cent.; lymphocytes, 36 per cent.; large mononuclears and transitionals, 3 per cent; (April 28): white blood count, 20,000; polymorphonuclears, 60 per cent.; lymphocytes, 34 per cent.; large mononuclears and transitionals, 6 per cent.; red blood count, 3,860,000; hemoglobin, 45 per cent.

Fig. 4.—Posterior view of tumor and right lung, with remnants of left lung below. Small metastasis on inner, posterior surface of right lung is to be noted, and photograph compared with Figure 1.

Necropsy Findings (April 30, fourteen hours postmortem).—The body was well developed and well nourished. Rigor mortis was complete in the extremities and lower jaw. There was nothing abnormal to be noted externally. No discharge was found at the external openings of the various tracts. The pupils were equal, and 4 mm. in diameter. The intraocular tension was very low.

Primary incision: This was limited to the chest by the restrictions of the permit. It extended from the suprasternal notch to a point a little below the ensiform cartilage, exposing a moderate layer of fat. The thorax was found to be wide and deep. The diaphragm was flush with the lower costal margin on the left and definitely flattened out. On the right, it was at the seventh

rib and normally dome shaped. This is interesting in view of the roentgen-ray findings, which indicated an abnormally high position of this organ on the left. On removal of the sternum, several cubic centimeters of a straw-colored fluid, with whitish-yellow masses of soft, puriform material floating in it, escaped, and a tumor mass presented over almost all of the region exposed.

The new growth was intimately adherent to the chest wall on the left and had forced the left lung downward and backward, compressing it until it was a mere mass of flabby, fleshy material. The heart was displaced to the right until its long axis lay almost in the midline, approximately vertical, the apex pointing slightly to the right. The right lung lay free in its pleural sac and was invaded but slightly by the tumor. As the latter is the most important structure encountered, it will be described first.

The tumor: This was roughly globular in shape, as can be seen from figures 3 and 4. It measured 10 cm. in its vertical, 9 cm. in its transverse and 8 cm. in its anteroposterior diameter. Its color was yellowish white; its surface

Fig. 5.—Transverse section of tumor at level of hilum. The esophagus, three bronchi and the pulmonary vessels will afford orientation.

coarsely nodular, and its consistence varied from firm to almost pultaceous. The thymus overlay the growth above and in front, forming a pinkish layer about 5 mm. thick, definitely separated from the yellowish mass of new growth behind and beneath it. Here and there nodules of the tumor penetrated to the anterior surface, forcing the thymic tissue aside.

The tumor, lungs and heart were removed in toto and in continuity. It was found that the first was composed of coarse nodules, averaging about 2 cm. in diameter in its upper part, and more homogeneous in its lower or main portion. The left parietal pleura was invaded extensively by infiltrating masses of soft pulpy tumor tissue, which tore away from the main growth when it was removed from the body.

Heart: This was removed from the pericardium, and it was found that the latter was quite free from any gross evidence of tumor infiltration and contained a small quantity of straw-colored fluid. The heart weighed 50 gm., and presented nothing at all abnormal.

Lungs: The right lung was preserved in continuity with the specimen, so that its weight cannot be given. It was slightly congested and moderately emphysematous, and presented two tumor metastases on its diaphragmatic sur-

face; one of these was discoid, 2 cm. in diameter, and about 5 mm. thick, obviously situated in the pleura. The other was larger, 1.5 cm. square, and pyramidal in shape, penetrating the lung tissue to a depth of 3 cm. or more, its apex directed toward the hilum. A third metastasis, shown in Figure 4, lay in the pleura near the hilum and slightly behind it. This was also discoid, 1 by 1 by 0.5 cm. in size. Otherwise, the organ was normal in appearance, the pleura smooth and shining and no other masses palpable. It is important to note that the hilum shows no enlargement of its lymph nodes. It was quite freely movable and normal on palpation.

The left lung was compressed until it was a mass of fleshy tissue and quite airless. Figure 5, showing a section through the hila of both lungs, reveals

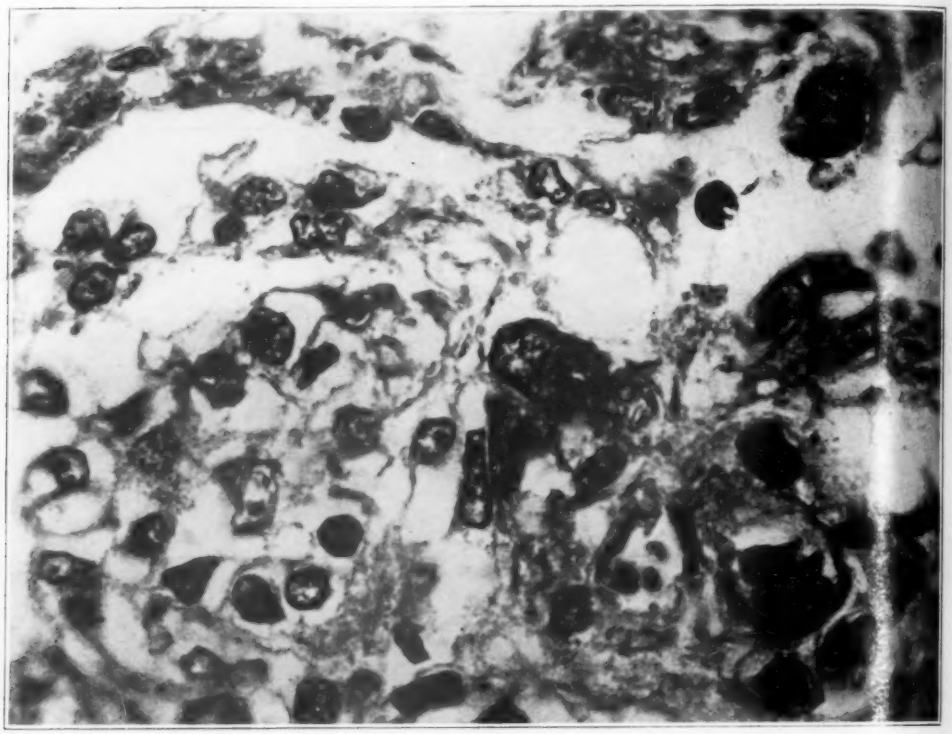

Fig. 6.—Photomicrographs of reticuloid type of growth, with rudimentary Hassal's corpuscle at right lower corner; × 650; hematoxylin-eosin stain.

how the tumor had invaded and replaced this organ by spreading downward along the inner aspect of the pleural lung capsule. It will also show the involvement of the esophagus, bronchi and pulmonary vessels at this level. Exploratory lung sections revealed moderately numerous areas resembling foci of lobular pneumonia, as microscopic examination proved them to be. Gross examination did not indicate whether or not they were tumor or inflammatory infiltrates, but it was thought that they were the former. The hilum of the lung was embedded, as shown in Figure 5, in dense masses of the tumor. It is to be noted that these metastases in the lung were all in the immediate vicinity of the primary growth and usually spread by infiltration rather than by true metastasis, a characteristic of this tumor.

Abdominal organs: The abdominal organs were removed by cutting away the diaphragm peripherally and severing the mesentery and rectum. It was noted that the liver was much enlarged, reddened and extended to the umbilicus. The spleen weighed 35 gm. It was almost as hard as stone, and its external surface was smooth and shining. On section, the parenchyma was found to be a deep purplish red, resembling porphyry. The pulp did not strip on the knife blade, and the malphighian corpuscles were indistinct; the trabeculae, vague. The picture was similar to that of cyanotic induration. The liver weighed 420 gm. Externally it was smooth and shining and rather pale brownish yellow. On section, much blood escaped from the widely dilated

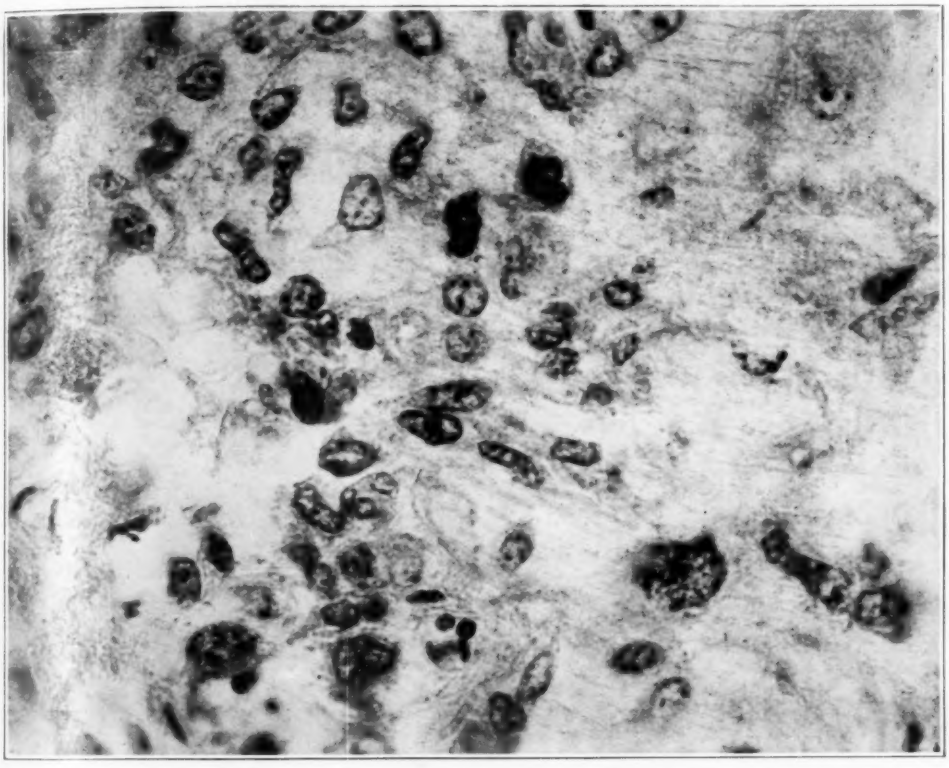

Fig. 7.—Photomicrograph of reticuloid type of growth; × 650; phosphotungstic acid hematoxylin stain.

hepatic veins, which sometimes attained a diameter of 75 mm. or more. The markings of the organ were indistinct, despite the passive congestion. The parenchyma was pale yellowish brown, and shining. The organ diminished in size after the blood was allowed to escape. The gallbladder contained a small quantity of brownish bile, readily expressible through the papilla of Vater. The gastro-intestinal tract presented nothing of note. The suprarenal glands were intensely congested in their medullary portions, blood escaping under pressure, on section. The mesenteric nodes were universally enlarged, some measuring as much as 2 cm. in long diameter. They were somewhat congested. The pancreas was not remarkable, nor were the kidneys.

The anatomic diagnosis was malignant thymoma of the anterior mediastinum, involving the left lung and, to a far lesser extent, the right; chronic passive congestion of the liver, spleen and suprarenal capsule, and chronic hyperplasia of the mesenteric lymph nodes.

Microscopic Examination.—The tumor was composed of cells which showed three definite types of growth: (1) a reticuloid, resembling the embryonic thymic reticulum; (2) an epithelioid, resembling an adenocarcinoma or a medullary carcinoma; and (3) a sarcomatoid, resembling a large, round cell lymphosarcoma or fibrosarcoma.

1. The reticuloid type. This was found in most of the sections examined and constituted the more typical pictures of the tumor. Sections from areas showing this form of growth showed a striking resemblance to Hammar's illustra-

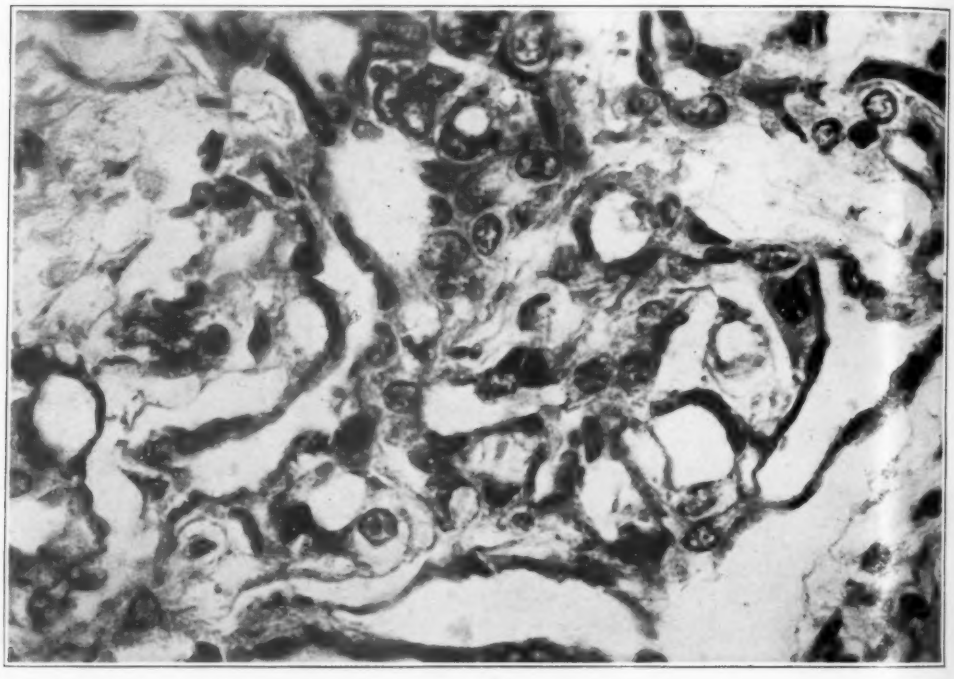

Fig. 8.—Epithelioid type of growth, ducts and reticulum; × 650; hematoxylin-eosin stain.

tion of the thymic reticulum in a 70 mm. embryo, as pictured in Ewing's textbook[3] (page 913). The cells were polyhedral, with a large, often lobulated, ovoid, vesicular nucleus, coarse and distinct nuclear network, and one or more distinct nucleoli, which stained pinkish with eosin. The cytoplasm was delicate and branching, the cells anastomosing freely with one another to form a delicate reticulum, which stained pink with eosin, red with acid fuchsin, and yellowish or reddish brown with phosphotungstic acid hematoxylin. Masses of reticulum formed innumerable alveolar structures in a meager connective tissue stroma. The average diameter of these cells was about 10 to 12 microns. Besides forming the reticulum, they frequently clumped together into masses which might be interpreted as immature Hassal's bodies, as they sometimes showed a slight tendency on the part of the cells to form concentric layers; but this was seldom

seen. Many tumor giant cells were found in this type of growth. Gigantic masses of lobulated nuclear material, or multiple nuclei occupied the greater part of the cell body, so that the cytoplasm was very inconspicuous. These cells measured from 18 to 20 microns. In Figures 6 and 7, two typical fields from the reticuloid portion of the tumor are shown. Figure 6 shows one of the masses of cells that might be interpreted as a very immature Hassal corpuscle.

2. The epithelioid type. This type of growth is shown in Figure 8. Here the cells were grouped into glandular complexes, which exhibited a tendency to form thin-walled and branching duct-like acini. Sometimes, the component cells were flat and elongated on section, sometimes cuboidal. In the former instance, they measured from 11 to 12 microns in length, and but 2 to 3 microns in thickness. In the latter, their diameter averaged about 8 microns. Their nuclei were spherical; stained deeply with nuclear dyes, and did not show the definite filamentous chromatic structure seen in the reticuloid variety. However, there were places where these ductlike structures faded imperceptibly into those of the reticular type, which often were associated with them. The stroma was made up largely of connective tissue, but parts of it were formed by the reticular tumor elements. No ciliated epithelium could be found in these ducts. Occasionally, a colloid secretion was encountered in connection with these, but it was present only in small quantities. In other parts of this type of growth, the cells, instead of forming ducts, were arranged in flat sheets, or masses, resembling those of a medullary carcinoma, without any tendency toward the formation of a reticulum.

3. The sarcomatoid form. This was met with in the pulmonary metastases, when the tumor had invaded the pleural connective tissue. Here, the cells were embedded discretely in dense, fibrous tissue, or lay in nests among its fibers, without anastomosing with one another. They were more or less spherical; averaged 8 microns in diameter, and possessed very little cytoplasm. They reminded one of some of the larger cells in the thymoma described by one of us,[2] resembling those of a lymphosarcoma that shows little maturity. The nuclei of these cells presented an appearance midway between that of the reticular cells and the epithelial duct cells, in that they were denser than those of the former, and less so than those of the latter. These portions of the tumor showed many enormous giant cells, often of very bizarre appearance and outline, which measured about 30 microns in length and from 18 to 20 microns in transverse diameter. Their nuclei were either lobulated or multiple, presenting groups of five or more. Another interesting feature about this type of growth was the presence of much fibrin in the form of thick fibrils that lay in groups between and about the cells, often forming a network, like small baskets. They always showed prominent nodal intersections and were best seen in the phosphotungstic acid hematoxylin sections.

Summary: In general, the tumor showed a great deal of necrosis, with a striking lack of vascularity, except where vessels already were present in the invaded tissue. In the necrotic areas, it was observed that the tumor formed halos of reticulum about the vessels, and that these zones faded off into the necrotic tissue on the one side and the vascular adventitia on the other, so that the effect was very misleading. If one had no other criteria for diagnosing the epiblastic character of the growth, one might have attributed an adventitial origin to this tissue. The tumor was evidently of extremely rapid growth, as mitotic figures were very abundant and present in all types of cells, the giant-cells presenting strange multiple mitoses in many instances.

Frozen sections stained with sudan III showed a large amount of sudanophil material, both in the cells of the stroma, where it appeared as coarse droplets, and in the cells of the ductlike and acinar structures. Nile blue sulphate showed this fatty material to be in part neutral fat, when present in coarse droplets, in part lipoid substances, when it was in the epithelium in the form of coarser or finer navy-blue granules. The presence of fats and lipoids in

this tumor indicates nothing more than an extensive degenerative infiltration. The lipoids were found in the healthier, the neutral fat in the more degenerated or in the necrotic portions, of the tumor.

Thymus: This was found to have been compressed and flattened. Hassal's corpuscles were very numerous and close together. Many of them showed cornification and invasion by leukocytes, as in involution, but most of them were of an immature type, mere collections of reticulum cells. There was a definite increase in the amount of reticulum, which was hypertrophic and compact. The eosinophil cells were not present in large numbers, but cells of the lymphocytic type were there in the usual amount. At the margin of the gland, where it was separated from the tumor only by its capsule, there was sometimes a still more marked increase in the reticulum, with its cells packed closely together. The only other feature that needs discussion is the presence of prominent strands of hyaline material that appeared to be connected with Hassal's bodies and radiated from them. It was composed of compacted reticulum. No tumor cells were found in the thymic sections examined, and no gradual transition from normal thymus to thymoma was observable.

Other organs: Little was discovered in the examination of the heart, liver, kidney, pancreas and suprarenal gland. Despite the gross evidence of passive congestion, there was little to indicate it in the microscopic sections. The spleen, however, was intensely congested, and the malpighian corpuscles were compressed and inactive. The trabeculae and capsule were somewhat thickened. The lungs showed the presence of the tumor and of the lobular pneumonia described in the gross. There was a marked purulent bronchitis and moderate passive congestion, with compensatory emphysema in some sections.

COMMENT

The clinical and pathologic features of this case are interesting. From the clinical standpoint, its chief appeal is the difficulty it presented to diagnosis. Perhaps the most striking point is the fact that the roentgen-ray examinations were not only of no assistance, but also were actually misleading, owing to the asymmetry of the growth and its encroachment on the left side. Roentgenograms of thymomas usually reveal shadows in the midline, in the mediastinal region. (Compare those of Ewing and Foot.) In this case, the distribution of the growth, with the compression and destruction of the left lung, combined to produce a shadow that was indistinguishable in location and outline from that thrown by an enlarged heart. A comparison of the roentgenograms and the photographs of the specimen will show at a glance why this was so, and how readily one might be mistaken in interpreting the roentgenograms. The roentgen ray also failed to demonstrate any marked irregularity of the shadows which might be construed as indicating the presence of a tumor.

No tumor cells were found in the fluid aspirated from the chest, although repeatedly sought for; and, although a new growth was suspected, no positive proof of its existence was forthcoming. The compression of the aorta and trachea gave signs and symptoms. The former produced a loud systolic murmur that directed the clinicians' attention to the heart, which proved to be normal. The transient

asphyxia and coughing caused by the latter was not enough evidence upon which to base a diagnosis of new growth. The blood counts and smears gave no assistance. It is strange that the compression of the esophagus by the tumor presented no difficulty to the passage of a stomach tube, which was readily introduced and withdrawn.

Pathology of the Tumor.—From the point of view of the pathologist, this tumor is of great interest. It is essentially epithelial in type, and it occurred in a baby, which alone stamps it as a rarity. The most important feature, however, is the light that it throws on the histogenesis of thymoma. Here, we have a tumor exhibiting a predominatingly reticular type of growth and substantiating Ewing's theory that thymomas not only arise from thymic reticulum, but may present a picture that is strikingly like normal embryonic thymus at an early stage of its development. Furthermore, the existence of glandular, or other definitely epithelial elements demonstrates the connection between this embryonal reticulum and the thymic carcinomas. That this ductlike growth represents remnants of the destroyed pulmonary tissue might be indicated; but the shading off of epithelium into reticulum, and the infiltrative and metaplastic character of the ducts would seem to render that hypothesis unlikely. The sarcomatoid portions of the growth need little discussion. They resemble the dissociated form of structure sometimes observed in carcinoma of the pancreas or cervix; but it is interesting to compare them with the so-called lymphosarcomas of the thymus, and note the striking resemblance.

That this tumor is epithelial is indicated by the following facts: 1. It resembles the reticulum of the thymus, which is ectodermal. 2. It forms definite glandular and alveolar masses of cells. 3. The production of cell complexes vaguely resembling Hassal's corpuscles also indicates ectodermal origin, although the structures produced are a very poor imitation of the finished corpuscles, and would scarcely serve as a means of identification if taken alone.

Of the four articles appearing since 1920,[7] only two were available, that of Symmers and Vance and that of Sweany. The latter is a short case report that describes a case of thymoma in conjunction with tuberculosis, and does not throw much additional light on the subject. Tuberculosis is so common that it might occur in conjunction with any tumor. If Symmers and Vance are correct (and we have no reason to doubt them), this is the fifth case of primary epithelial thymoma to be reported and the only one occurring in a child. Our reasons for

7. Cleland, J. B., and Beare, F. H.: M. J. Australia **1**:182 (Feb. 18) 1922. Harvier, P.: Bull. et mém. Soc. méd. de hôp. de Paris **45**:874 (March 18) 1921. Symmers, Douglas, and Vance, B. M.: Footnote 4. Sweany, H. C.: Primary Tumor of Thymus Associated with Tuberculosis, J. A. M. A. **80**:754 (March 17) 1923.

believing it to be epithelial have been stated. We think that it is primary because: it occupied the region of the thymic center (anlage); spread by direct extension rather than by metastasis; limited its extension chiefly to the pleura, and did not invade the pulmonary alveoli so far as we could ascertain. Most important is the fact that it gave no evidence that it had originated from any other organ that could bequeath to it the morphology shown by its cellular elements, which resembled embryonic thymus more closely than anything else. Our tumor does not correspond very closely with those that have been reported in older persons, but there is no reason why it should, as malignant epithelial tumors occurring in childhood are notoriously different from those appearing in old age.

We have retained the term thymoma for the reason that it is descriptive, while the more usual term "carcinoma" is not. Although the origin of thymomas is ectodermal, possibly in all cases, and certainly so in that of the epithelial tumors, the term carcinoma is, we think, misleading in a tumor of this type, which approaches the embryoma so much more closely in its morphology and in its variability of cell types, although it could not be one. We believe that in calling this tumor a carcinoma, one fails to indicate the polymorphic tendencies of its component cells; just as we believe that the term lymphosarcoma should not be used in connection with the lymphocytoid type of malignant thymoma, until it is proved that it is indeed a neoplasm of the lymphatic system. We would suggest some such term as thymic epiblastoma as appropriate, brief and indicative of the origin and the embryonal character of the growth. It could be applied to the lymphocytoid tumors only when they were sufficiently unlike lymphosarcomas to warrant it, or as soon as the ectodermal origin of the small thymic cells has been determined beyond a doubt.

PRELIMINARY REPORT ON THE KOTTMANN REACTION IN CHILDREN

WITH A NOTE ON THE TREATMENT OF CHOREA WITH THYROID *

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Kottmann [1] first described his test for thyroid activity in 1920. He had previously studied the serum in pregnancy, and from this work assumed that certain physicochemical differences must be present in the serums of patients suffering from thyroid dysfunction. Petersen, who first investigated the test in this country, thus describes the process:

> Because of the peculiar relation of iodin to the glandular metabolism, he (Kottmann) began his experiments with colloidal iodin preparations, using silver iodid for this purpose because of its well known photosensitivity. In the test as developed by him, certain phenomena commonly observed in photography play a rôle. Thus, when silver nitrate is added to potassium iodid, silver iodid is formed. In the presence of a protective colloid, the growth of the particles is retarded, depending on the protective property of the colloid used. In the photographic plate, a gelatin preparation is used for this purpose, and the prepared film (silver iodid or bromid dispersed in gelatin) is permitted to ripen. During this process of ripening, the colloidal particles of the silver salt gradually become larger, and as they do so, they become more photosensitive than when in the original highly dispersed state. If we substitute serum for the gelatin, a similar reaction might be anticipated, the particles of silver iodid formed becoming larger or smaller according to the protective property of the serum. The greater the photosensitivity of the silver iodid, the poorer the protective property of the serum used, and presumably, therefore, the coarser the colloidal dispersion of the serum itself. The less photosensitive the silver iodid, the greater the protective power of the serum and presumably the greater the state of dispersion of the serum colloids themselves.

Kottmann himself found that, in cases of exophthalmic goiter, there was a definite, and, in severe cases, a marked, change in the reaction compared to that found in control cases. Petersen [2] and others in a series of 400 cases obtained markedly retarded reactions in sixty-five

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* From the Children's Medical Division of Bellevue Hospital.

1. Kottmann, K.: Colloidal Chemical Studies of Thyroid Gland Problems, Schweiz. med. Wchnschr. **30**:644 (July 22) 1920.

2. Petersen, W. F.; H'Doubler, F. T.; Levinson, S. A., and Laibe, J. E.: The Kottmann Reaction for Thyroid Activity, J. A. M. A. **78**:1022 (April 8) 1022; Studies in the Kottmann Reaction for Thyroid Activity, Arch. Int. Med. **30**:386 (Sept.) 1922.

of the seventy cases of hyperthyroidism, and in eleven cases under bromid medication, thus confirming Kottmann's observations in these conditions. In the serums of patients with acute infections, Petersen found normal reactions in all except one, which was slightly retarded, and several accelerated reactions which occurred in the more severe infections. From his observations in this series, Petersen considers that the Kottmann reaction yields a close index of thyroid function. Kottmann found accelerated reactions in cases of goiter, but Kay [3] felt that the test failed in cases of hypothyroidism, although it gave definite indication of hyperthyroid conditions. He found that it checked with the clinical findings and basal metabolism. Petersen also studied the test in experimental conditions, and concluded that alterations obtained in the reaction "need not be associated with thyroid dysfunction. The thyroid dysfunction alters cellular metabolism and this in turn alters the physical properties of the serum so that in cases of hyperthyroidism the serum is a better protective agent than normally. If the cellular metabolism is altered by other insults, serum alterations must also take place, and these will be reflected in the Kottmann reaction."

Since no references were found as to the Kottmann reaction in children, this investigation was undertaken in the children's medical division at Bellevue hospital under the direction of the department of diseases of children at Columbia University, in the hope of discovering a means of differentiating between the various types of endocrine disturbance in the early stages.

TECHNIC

To 1 c.c. of clear serum is added 0.25 c.c. of a 0.5 per cent. solution of potassium iodid and 0.3 c.c. of a 0.5 per cent solution of silver nitrate. The tube is rotated gently, and then exposed for five minutes to a 500 watt Mazda lamp at a distance of 25 cm. Then 0.5 c.c. of a 0.25 per cent. solution of hydrochinon is added, and the color changes are noted. The final color is a dark reddish brown. Although theoretically the developing should be done in a dark room, the use of diffused daylight apparently did not alter the results. Normally, the reaction is complete in about ten minutes, and a reaction which is complete in about five minutes is considered accelerated. The specimens of blood were all taken in the morning, either with the patient fasting or about four hours after the morning meal.

GROUPS

For purpose of comparison, the 106 cases in which the reaction was studied were arranged in five groups. Group 1, the controls, was composed of twenty-eight children who showed no evidence of thyroid

3. Kay, W. E.: A Study of One Hundred Cases Diagnosed as Hyperthyroidism, J. A. M. A. **79**:2149 (Dec. 23) 1922.

disturbance or of infection. The second group comprised thirty-three cases of acute infection; Group 3 was composed of eleven cardiac cases, and Group 4 consisted of thirteen cases diagnosed clinically as endocrine disturbances, and six cases of idiocy. The cases of chorea were put in a group (Group 5) alone because of the interesting results obtained, and will be considered in detail. The patients ranged from a 3 weeks old infant with eczema to children of 12 years.

RESULTS

In Group 1 (Table 1), twenty-one of the twenty-eight reactions were normal. No particular explanation could be made for the two slightly accelerated and the two slightly retarded reactions, nor for one of the three which were markedly retarded. One of these three

TABLE 1.—*Miscellaneous Conditions (Group 1)*

Diagnosis	Number of Cases	Slightly Accelerated	Accelerated	Normal	Slightly Retarded	Retarded
Epilepsy	2	1	..	..	..	1 (bromid)
Rickets	11	1	.	8	2	..
Spastic paraplegia	1	..	..	1	..	..
Convalescent; pneumonia	3	..	..	2	..	1 (calcium chlorid)
Foundling	1	..	..	..	..	1
Convalescent; tonsillitis	1	..	..	1	..	..
Contracture of hand	1	..	..	1	..	..
Talipes equinus	1	..	..	1	..	..
Fracture of arm	1	..	..	1	..	..
Club foot	1	..	..	1	..	..
Chlorosis	1	..	..	1	..	..
Mercury poisoning	1	..	..	1	..	..
Diet regulation	1	..	.	1	..	..
Eczema	1	..	..	1	..	..
Well child	1	..	..	1	..	..
Total	28	2	..	21	2	3

patients, an epileptic, had been given bromids for a severe convulsion several hours previously, and the other, an infant who was recovering from a severe pneumonia, had been given calcium chlorid for two weeks consecutively. This last observation is interesting because of the findings of Kottmann, Petersen and Merke[4] that bromids prolong the reaction, and of Petersen that the administration of iodids also retards the reaction although in less degree.

In Group 2, the acute infections (Table 2), it will be noted that only thirteen of the thirty-three reactions were normal. Of the accelerated reactions, eleven occurred in children with severe infections, three of whom died subsequently, and one, who suffered from septicemia, went through a long illness, and in fact has not yet recovered. No special reason was found for the two slightly retarded or two

4. Merke, F.: Schweiz. med. Wchnschr. **51**:200 (March 3) 1921 (referred to by Petersen).

of the markedly retarded reactions. The child with encephalitis who gave a retarded reaction and who later died had been given sodium bromid for extreme restlessness. In his first paper, Petersen suggested that border line cases, such as those of tuberculosis would be a fruitful field of investigation in relation to the Kottmann reaction. Hence it is interesting to note that one of our two cases of pulmonary tuberculosis showed an accelerated reaction, and that the other was slightly accelerated.

Group 3 (Table 3), the endocrine and idiocy cases, is entirely too small to permit of conclusions. It was also unsatisfactory because most

TABLE 2.—*Acute Infections (Group 2)*

Diagnosis	Number of Cases	Slightly Accelerated	Accelerated	Normal	Slightly Retarded	Retarded
Meningitis	3	..	..	2	1	..
Bronchopneumonia	2	..	2	..	..	..
Tuberculous meningitis	1	..	1	..	..	..
Pneumonia	5	1	1	3	..	..
Bronchitis	3	..	..	1	1	1
Tonsillitis	1	..	..	1	..	..
Acute rheumatic fever	1	..	1	..	..	..
Septicemia	1	..	1	..	..	..
Influenza	6	..	3	2	..	1
Encephalitis	5	..	2	2	..	1
Acute nephritis	3	1	..	2	..	..
Pulmonary tuberculosis	2	1	1	..	..	..
Total	33	3	12	13	2	3

TABLE 3.—*Endocrine and Idiocy Cases (Group 3)*

Diagnosis	Number of Cases	Slightly Accelerated	Accelerated	Normal	Slightly Retarded	Retarded
Hypopituitary	6	..	1	5	..	..
Thymus and microcephalus	1	..	..	1	..	..
Cretin	2	1	1	..	..	..
Hyperthyroid	2	1	..	..	..	1
Goiter	1	..	1	..	..	..
Dyspituitary	1	..	..	..	..	1
Idiots	6	1	1	4	..	..
Total	19	3	4	10	..	2

of the cases were sent to us from the outpatient department, and had not been under our own observation, so that we had no method of control. Also, most of them had been under treatment with various glandular preparations for varying lengths of time. Only ten of the nineteen children had normal Kottmann reactions. One, who had clinically a fairly definite case of hyperthyroidism, gave the characteristically retarded reaction, and the child with the enlarged thyroid who gave an accelerated reaction nearly fainted during the blood taking. The two cretins are also of interest. One, a boy of 6, who had been taking thyroid intermittently for several years, gave a slightly accelerated reaction. The other, an infant of 14 months in very poor physical

condition, at first gave an accelerated reaction; but later, after three weeks of thyroid therapy, followed by distinct clinical improvement, gave a normal reaction.

Group 4, the cardiac cases (Table 4), was rather interesting. The three patients who gave normal reactions were in fairly good general condition, and two were up and about the ward. In the remainder of the eleven cases, with one exception, although they were compensated, the patients were all pale and undernourished, as is usual in these cases while in the hospital. The child with the slightly retarded reaction had pericarditis with effusion at the time the blood was taken, and had been receiving morphin for some time. Incidentally, two of the children with accelerated reactions were noted as being "stupid" and having enlarged thyroids. How much this may have had to do with the results of the test, it is impossible to state.

TABLE 4.—*Groups 4 and 5*

Diagnosis	Number of Cases	Slightly Accelerated	Accelerated	Normal	Slightly Retarded	Retarded
Cardiac cases	11	1	6	3	..	1 (morphin)
Chorea cases	15	1	9	4	1	..

RESULTS IN CHOREA CASES

The chorea cases (Table 4) proved unexpectedly to be of great interest to us. It will be seen from the table that nine of the fifteen cases had accelerated reactions, and that one had a slightly accelerated Kottmann reaction. Only four were normal, while one was slightly retarded. Of the normal reactions, two occurred in mild cases, and one in a convalescent. The third was obtained in a case which was mild on admission, but which became worse later and then gave an accelerated reaction. This child improved after a time, and again gave an accelerated reaction, but when she developed an acute tonsillitis with exacerbation of the choreiform movements, the Kottmann reaction was again accelerated. The child with the slightly retarded reaction had a mild case and was in the convalescent stage. On analyzing these results, then, we found that the severe or moderate cases of chorea consistently showed accelerated Kottmann reactions.

In order to observe the effect of the Kottmann reaction of thyroid administration by mouth, we selected one of these children as an experimental subject, merely because he was likely to be in the hospital for some time. He had already been in hospital over a month under the usual treatment of isolation and high calory diet, with no abatement of his symptoms. After thyroid extract had been given for three days, there was a marked diminution in his formerly incessant movements, and within a week he appeared perfectly normal. This was confirmed by

several observers. As a result, thyroid was given in eight other cases, and equally striking results were obtained in five. The three other children had the type of chorea in which extreme weakness and psychic disturbance are the predominating symptoms. One of them was a 5-year-old girl who, on admission to the hospital a month before, was unable to sit up. At the time thyroid was started, she was improved to the extent that she could sit up alone, but still had choreic movements and was very weak. After receiving thyroid for nearly three weeks, she seemed better but was unable to stand. The dose was therefore increased, and three days later, the child was found walking up and down her bed entirely unsupported. Whether this was a result of thyroid therapy or a coincidence we are not willing to say, but from that time on improvement was rapid. At present, twelve children with chorea have been or are being treated with thyroid. It is still far too early to make any statements as to the results of this method of treatment, or as to suitable dosage.

If, as Petersen suggested, the Kottmann reaction is a reflection of the increased metabolism which occurs with hyperthyroidism, then an accelerated reaction would be expected, with a decreased basal metabolism. In a condition such as chorea, in which the patient is in almost constant motion, we would anticipate an increased basal metabolism. This, however, would be difficult if not impossible to determine. If this reasoning is correct, the administration of thyroid to these patients is not a reasonable procedure; but, on the other hand, we have the evidence of accelerated Kottmann reactions. Other factors are doubtless involved, such as disturbance of the nervous system from an abnormal physiologic condition of the glands of internal secretion. The field of speculation which has thus been opened is a wide one, demanding careful study. With the clues thus furnished us from this preliminary work, we are now studying chorea particularly from this point of view. As yet, we can say little about dosage, but this is being carefully considered, as well as the advantages of using various preparations of thyroid, such as thyroxin, thyroid extract and thyroid residue. The indications are that the cases characterized by great weakness and psychic disturbance require larger doses of thyroid. We realize that our findings are far from conclusive, but we feel that the results of this method of treatment have been sufficiently striking to warrant at least a hope that we have chanced on a way to shorten the course of chorea. The final test will be a comparison of the disease in those patients who have been given the ordinary treatment with those who have in addition received thyroid.

SUMMARY

The Kottmann test was performed on 106 children.

Twenty-eight children presenting miscellaneous conditions were chosen as controls, of whom twenty-one were normal. Of the three retarded reactions, two could be explained on the basis of medication (sodium bromid and calcium chlorid).

Of thirty-three cases of acute infection, only thirteen gave normal Kottmann reactions.

The group of endocrine cases was unsatisfactory, and no conclusions could be drawn from the results.

In the group of cardiac cases, the predominating reaction was acceleration, probably from the lowered vitality of the children.

Because of the findings in the fifteen cases of chorea, administration of thyroid is suggested as a possible aid in treatment.

THE TREATMENT OF INFANTILE TETANY WITH ULTRAVIOLET RADIATION

ITS EFFECT ON THE CLINICAL SYMPTOMS AND ON THE CALCIUM CONCENTRATION IN THE BLOOD SERUM *

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As a result of the many investigations on the pathogenesis of infantile tetany, various remedial agents have been suggested for its treatment. Temporary starvation, catharsis and change from cow's milk to maternal milk have all been employed, but at present are usually considered accessory to more potent measures. The effect of cod liver oil with and without phosphorus has been more completely studied, and gradual but rather slow improvement demonstrated. Howland and Marriott,[1] in 1918, placed the therapeutic use of calcium on a scientific basis by showing that, in active infantile tetany, the calcium concentration in the blood serum is uniformly low and that this concentration can be increased by the administration of sufficient doses of calcium salts. It is a recognized fact that, even with combined cod liver oil and calcium therapy, the return of the serum calcium to a normal figure may be very slow, although the clinical findings of tetany may disappear fairly promptly (as in Case D. G., Table 3). The demonstration of a low concentration of calcium in the blood serum is therefore a valuable aid in the diagnosis of infantile tetany, and the demonstration of its return to normal is probably the most reliable sign of the cure of the disease.

OPINION OF OTHERS AS TO TREATMENT

Many clinicians have felt that the chlorid of calcium is more effective than the lactate in the treatment of infantile tetany, and Howland and Marriott [1] substantiated this clinical impression. This observed fact has been proved by Gamble and Ross [2] to be due to the unoxidizable chlorin-ion (Cl). This is in agreement with the fact demonstrated by Scheer [3] that placing hydrochloric acid in the milk will cause the

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* From the Infant's Hospital, The Children's Hospital and the Department of Pediatrics, Harvard Medical School.

1. Howland, John, and Marriott, W. McK.: Quart. J. Med. **11**:289 (July) 1918.

2. Gamble, J. L., and Ross, G. S.: Studies of Tetany. II, Am. J. Dis. Child. **25**:470 (June) 1923.

3. Scheer, K.: Jahrb. f. Kinderh. **97**:130 (Feb.) 1922.

symptoms of infantile tetany to disappear, and is also in agreement with the finding of Freudenberg and György [4] that the same result follows the administration of ammonium chlorid. Freudenberg and György [5] assumed that the therapeutic action of ammonium chlorid was due to the acid effect which Haldane [6] has demonstrated that this salt produces. Gamble and Ross have shown that ingestion of calcium chlorid, hydrochloric acid or ammonium chlorid produces the same acid effect in the body, this effect consisting of a reduction of the plasma bicarbonate due directly to an increase in the chlorids, and an elevation of the hydrogen-ion concentration of the plasma. On the basis of data published by Rona and Takahashi [7] in 1913, Freudenberg and György pointed out that a reduction of the bicarbonate and an increase in the hydrogen-ion concentration in the plasma might be expected to increase the ionized fraction of the total calcium content of the plasma. This increase in effective calcium should decrease the hyperirritability of the neuromuscular apparatus.

The relief of the symptoms of infantile tetany by the methods mentioned is either slow, with a rather long period of active symptoms; or when the hydrochloric acid producing substances are used, it is rapid but of short duration, the hyperirritability tending to recur very soon after cessation of medication. A procedure leading to more permanent results would be very acceptable in the treatment of the disease. The fact that tetany usually occurs in late winter and early spring, when the concentration of the actinic rays of the sun is low, and is spontaneously cured in the early summer, suggested an investigation of the effects produced by the use of ultraviolet radiation. Climatic conditions precluded the employment of the sun's rays. Park [8] and others have shown that, in rickets at least, the effect of cod liver oil in curing or protecting against the disease is the same as that secured by the use of sunlight. Because of this interchangeable effect on an associated disease, a few patients with active tetany symptoms and some with a low serum calcium concentration accompanying rickets were given varying doses of cod liver oil, to serve as comparison cases.

Huldschinsky,[9] considering infantile tetany as a manifestation, in the nervous system, of rickets, showed, in 1920, that this "cerebral rickets" could be relieved by the use of ultraviolet rays in the same way that he had already proved the bone pathology to be influenced.

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4. Freudenberg, E., and György, P.: Klin. Wchnschr. **1**:410 (Feb. 25) 1922.
5. Freudenberg, E., and György, P.: Jahrb. f. Kinderh. **96**:5, 1921. Freudenberg, E., and György, P.: Klin. Wchnschr. **1**:222 (Jan. 28) 1922.
6. Haldane, J. B. S.: J. Physiol. **55**:265 (Aug.) 1921.
7. Rona, P., and Takahashi, D.: Biochem. Ztschr. **49**:370, 1913.
8. Park, E. A.: Physiol. Rev. **3**:106 (Jan.) 1923.
9. Huldschinsky, K.: Ztschr. f. Kinderh. **26**:207 (Sept.) 1920.

Sachs [10] reported independently, and at the same time, the clinical cure of seven cases of latent infantile tetany by the employment of artificial sunlight, and later, he [11] published the records of eight patients clinically cured of active tetany by the same means. Both authors used as their criteria for diagnosis and improvement the mechanical and electrical hyperirritability of peripheral nerves. The only published observations concerning the effect of ultraviolet radiation on serum calcium were reported nearly simultaneously by Tisdall [12] and Kramer, Casparis and Howland,[13] working on the inorganic phosphorus and calcium content of the serum in cases of healing rickets. The latter authors record one case of infantile tetany, in which, however, calcium therapy had been employed for nearly one month before active ultraviolet irradiation began. Ten of the total of eleven reported cases of rickets showed an increase in the serum calcium concentration under artificial heliotherapy, this being coincident with the inorganic phosphorus increase. In none of the cases was the serum calcium below 8 mg. in 100 c.c. at the beginning of treatment.

PRESENT STUDY OF CASES

The present study is based on eleven cases of infantile tetany treated with ultraviolet rays and four comparison cases selected from among those patients who received cod liver oil. The usual criteria of mechanical and electrical hyperirritability, accompanied by a low serum calcium concentration, were used in making the diagnosis and following the progress. The demonstration of mechanical hyperirritability consisted in eliciting an appropriate muscular contraction by tapping the trunk of the facial nerve (facial phenomenon of Chvostek) or the peroneal nerve, or producing carpal spasm by compression of the upper arm (Trousseau). The electrical irritability was studied in the usual way with the galvanic current (Erb's test). A cathodal opening contraction (COC), or, in its place, a cathodal closing tetany (CCT), below 5 milliamperes was considered as the electrical sign of greatest diagnostic importance. In the presence of such a finding, the anodal opening contraction (AOC) was obtained with less current than the anodal closing contraction (ACC), the so-called reversal of anodes (AOC < ACC). The occurrence of this latter phenomenon, even in the absence of a cathodal opening contraction (COC) below 5 milliamperes, was considered as suggestive evidence for the diagnosis of latent tetany.

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10. Sachs, F.: Jahrb. f. Kinderh. **93**:167, 1921.
11. Sachs, F.: München. med. Wchnschr. **68**:984 (Aug. 5) 1921.
12. Tisdall, F. F.: Canad. M. A. J. **12**:536 (Aug.) 1922.
13. Kramer, Benjamin; Casparis, H. R., and Howland, John: Ultraviolet Radiation in Rickets, Am. J. Dis. Child. **24**:20 (July) 1922.

Those patients who came with a history of very recent convulsions, carpopedal spasm or laryngospasm, or showed these symptoms in the hospital, and who had a serum calcium below 7 mg. in 100 c.c., were classified as active cases (Table 1). Those patients without manifest symptoms, but who showed recognizable hyperirritabiliy signs, were classified as latent cases (Table 2). The latter varied greatly in severity, two having a moderately low serum calcium concentration with no signs of hyperirritability but reversal of the anodes in Erb's test.

The criterion used to indicate complete cure of the disease was the return of the blood serum calcium concentration to practically the normal figure of 10 mg. in 100 c.c., with the method published by Kramer and Tisdall [14] in 1921. As was previously pointed out, this standard is more exacting than the clinical estimation of a cure. In some of the later cases, measurements were made of the inorganic phosphorus concentration in the serum by the method of Tisdall,[15] or in the whole blood by the method of Bell and Doisy.[16]

The source of the ultraviolet rays was an all-mercury electrode, quartz-encased burner, using 4 amperes on a 110-volt direct circuit. The age of this lamp was between 100 and 200 production hours during the course of this study. About 65 to 67 per cent. of the total radiation of this type of burner consists of ultraviolet rays. Although the spectrum of the particular burner used was not studied, Coblentz [17] has shown that the liquid mercury electrode burner produces ultraviolet radiation with the most intense spectral lines at 365, 405, 314 and 302 millimicrons in decreasing magnitude. Hess and Weinstock [18] have recently shown that the rays with a wave length of 302 millimicrons or less are the most active in their curative and protective effects on rats living under a rickets producing regimen. In this connection, it is interesting to note that the intensity of the sun's ultraviolet spectrum as analyzed by Abbott and Fowle [19] closely approaches zero at a wavelength of 300 millimicrons.

TECHNIC

The patients all were exposed with the lamp at a uniform and unvarying distance of 50 cm. from the surface of the body. The initial treatment was usually two minutes to the front and two minutes to the back of the body (total of four minutes), and this was increased one

14. Kramer, Benjamin, and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921.
15. Tisdall, F. F.: J. Biol. Chem. **50**:329 (Feb.) 1922.
16. Bell, R. D., and Doisy, E. A.: J. Biol. Chem. **44**:55 (Oct.) 1920.
17. Coblentz, W. W.: Am. J. Electrother. & Radiol. **39**:395 (Oct.) 1921.
18. Hess, A. H., and Weinstock, Mildred: Study of Light Waves in Their Relation to Rickets, J. A. M. A. **80**:687 (March 10) 1923.
19. Abbott and Fowle: Ann. Astrophys. Obs. **2**:104, 1908.

minute to the front and to the back daily (total increase of two minutes), unless contraindicated by erythema. The maximum total exposure in this clinic never exceeds forty minutes daily, and this was not reached in any of the cases studied. The skin of a few of the patients became moderately pigmented, and nearly all of them showed slight desquamation at some stage of the treatment. The burner used

TABLE 1.—*Active Cases of Infantile Tetany Treated with the Mercury Vapor Quartz Lamp at a Distance of 50 Cm.**

Patient, Age and Color	Date, 1923	Symptoms	Electrical Reaction. Milliamperes	Mg. in 100 C.c.		Total Minutes Treatment
				Ca	P	
P. B. 5 mo. White	3/28	Conv., fac. 0, crow +	CCT 5.0, AOC < ACC	5.5	—	0
	4/ 4	Fac. ±, crow 0	CCT 7.0, AOC < ACC	—	—	10
	4/ 6	None	COC 7+, AOC < ACC	8.4	—	20
	4/10	None	COC 7+, ACC < AOC	9.3	—	64
M. S. 8½ mo. White	4/15	Conv., crow 0, fac. ±	CCT 5.0, AOC < ACC	6.8	—	0
	4/19	Fac. ±, no conv.	CCT 6.5, AOC < ACC	—	—	18
	4/23	None	COC 7+, AOC = ACC	8.5	—	40
	4/28	None	COC 8+, ACC < AOC	9.6	—	74
R. C. 9 mo. White	4/25	Conv., fac. +, Trou. +	CCT 2.5, AOC < ACC	5.4	—	0
	4/28	Conv., fac. +, crow +	CCT 3.5, AOC < ACC	—	—	18
	4/30	Fac. ±, crow +	CCT 5.0, AOC < ACC	6.6	—	26
	5/ 4	Crow +	CCT 7.0, AOC < ACC	8.0	4.1(WB)	94
	5/11	None	COC 7+, ACC < AOC	9.5	6.0(WB)	224
	5/18	None	COC 7+, ACC < AOC	10.0	—	224
D. A. 5 mo. White	5/ 4	Laryngospasm, fac. +, Trou. +	COC 2.5, AOC < ACC	5.4	6.4(WB)	0
	5/ 8	Fac. +, crow +	COC 7.5, AOC < ACC	—	—	18
	5/11	Fac. 0, crow ±	COC 6.0, AOC < ACC	7.7	8.1(WB)	38
	5/17	None	COC 7+, ACC < AOC	9.8	6.2(S)	110
C. R. 12 mo. White	5/10	Conv., fac. +, crow +, Trou. +	COC 3.0, AOC < ACC	5.9	5.8(WB) 8.1(S)	0
	5/14	Crow +, fac. ±	—	7.9	—	26
	5/18	None	COC 7+, AOC < ACC	—	6.4(S)	66
	5/23	None	COC 7+, ACC < AOC	8.1	8.3(S)	94
	5/28	None	—	9.7	6.8(S)	250
A. R. 6 mo. Colored	5/14	Conv., fac. +, crow +, Trou. +	CCT 3.5, AOC < ACC	—	6.3(S)	0
	5/15	Crow, fac., Trou. +	CCT 6.0, AOC < ACC	5.2	—	6
	5/18	Crow, Trou. ±, fac. 0	CCT 7.0, AOC < ACC	7.5	—	34
	5/23	None	COC 7+, AOC = ACC	7.8	6.6(S)	114
	5/28	None	COC 7+, AOC = ACC	9.3	—	244

* In the tables, Ca = calcium; P = inorganic phosphorus; conv. = convulsion; fac. = facial phenomenon (Chvostek); Trou. = Trousseau's phenomenon; CCT = cathodal closing tetany; COC = cathodal opening contraction; AOC < ACC = anodal opening contraction with less current than anodal closing contraction; (WB) = whole blood; (S) = serum; HCl = hydrochloric acid; C.L.O. = cod liver oil; $CaCl_2$ = calcium chlorid; NH_4Cl = ammonium chlorid.

was shown, near the end of the series, to produce a mild erythema of the previously unexposed skin of an infant's abdomen in four minutes at a distance of 50 cm.

None of the eleven patients treated received cod liver oil, calcium, ammonium chlorid or other medication directed toward the relief of the tetany. They were kept away from open windows and were not

taken out doors. All received whole cow's milk or its indicated dilution, and those of proper age received cereal. Green vegetables and orange juice were withheld during the immediate period of observation.

The progress of the active cases of infantile tetany treated with ultraviolet radiation is recorded in Table 1, and the latent cases in Table 2. The data on two patients with active teany who received cod liver oil are given in Table 3. In Table 4 are recorded the calcium

TABLE 2.—*Latent Cases of Infantile Tetany Treated with the Mercury Vapor Quartz Lamp at a Distance of 50 Cm.*

Patient, Age and Color	Date, 1923	Symptoms	Electrical Reaction, Milliamperes	Mg. in 100 C.c.		Total Minutes Treatment
				Ca	P	
C. McG.	4/ 3	Crow +, fac. +	CCT 2.5, AOC < ACC	6.9	—	0
6 mo.	4/ 6	None	CCT 5.0, AOC = ACC	—	—	12
White	4/10	None	COC 7+, AOC = ACC	8.9	—	48
	4/15	None	COC 7+, ACC < AOC	—	—	84
	4/20	None	COC 7+, ACC < AOC	10.7	—	126
	5/11	None	COC 7+, ACC < AOC	10.3	7.6(S)	378
S. S.	5/ 3	Crow +, fac. +, Trou. +	CCT 5.0, AOC < ACC	7.4	5.5(WB)	0
3½ mo.	5/ 5	Crow +, fac. +, Trou. ±	—	7.6	—	4
White	5/11	None	COC 7+, ACC < AOC	8.6	5.1(WB) 5.4(S)	54
	5/18	None	COC 7+, ACC < AOC	9.4	6.7(S)	142
	5/22	None	—	10.5	—	242
S. P.	5/ 4	None	COC 5.0, AOC < ACC	6.2	3.4(WB)	0
9 mo.	5/ 8	None	COC 7+, AOC < ACC	—	—	10
White	5/11	None	COC 7+, AOC < ACC	7.4	4.3(WB) 6.3(S)	40
	5/18	None	COC 7+, AOC = ACC	8.8	6.0(S)	142
	5/23	None	—	9.5	—	186
U. W.	5/ 7	None	COC 7+, AOC < ACC	6.9	—	0
12 mo.	5/ 8	None	COC 7+, AOC < ACC	7.2	2.1(WB)	0
Colored	5/14	None	—	8.3	2.7(WB)	58
	5/18	None	COC 7+, AOC = ACC	8.6	5.7(S)	112
	5/23	None	COC 7+, ACC < AOC	8.8	4.2(S)	192
	5/28	None	COC 7+, ACC 7+, AOC 7+	9.9	—	300
S. R.	5/10	Crow +, fac. ±	COC 7+, AOC < ACC	6.7	4.7(WB) 6.3(S)	0
2¼ yr.	5/14	Crow +, fac. 0	—	6.1	6.5(S)	10
White	5/17	Skin erythema	—	—	—	28
	5/18	Skin erythema	COC 7+, AOC = ACC	—	—	32
	5/23	None	COC 7+, ACC < AOC	8.9	6.4(S)	37
	5/28	None	—	9.5	6.4(S)	76

determinations on the blood of two patients with rickets who showed moderately low serum calcium concentrations and who were also receiving cod liver oil.

RESULTS

The six active cases of infantile tetany (Table 1) all showed steady clinical improvement with ultraviolet irradiations, as evidenced by the relief of symptoms and the decrease in mechanical and electrical hyperirritability. Only one patient had a convulsion after the first treatment, and this was inadvertently induced by a gastric lavage. The clinical improvement was paralleled by the steady increase in serum calcium

concentration. This had reached a practically normal figure in each patient at the time of discharge or when the observations were discontinued. With the mercury vapor lamp at the uniform distance of 50 cm., the total length of exposure necessary to cause an increase of 1 mg. of calcium in 100 c.c. of serum varied from seventeen to sixty-five minutes, with an average of forty-one minutes. The rise of calcium was proportionately more rapid in those patients who had the lowest concentrations in the serum at the beginning of the irradiations. The average number of days under treatment was thirteen. The mechanical hyperirritability symptoms disappeared in from four to eight days.

TABLE 3.—*Active Cases of Infantile Tetany Treated with Cod Liver Oil*

Patient, Age and Color	Date, 1923	Symptoms	Electrical Reaction, Milliamperes	Medication	Ca. Mg. in 100 C.c.
A. C. 4 mo. White	2/20	Conv., carpopedal spasm	CCT 2.0, AOC < ACC	None	5.6
	2/22	Same	—	HCl, 630 c.c. tenth normal daily	—
	2/24	No conv., Trou. 0	COC 7+, AOC < ACC	Omitted	—
	3/ 1	Fac. +, Trou. +	CCT 2.5, AOC < ACC	Lactic acid milk; C. L. O., 4 c.c. daily	7.1
	3/26	None	COC 6.0, ACC < AOC	Same	8.8
	3/30	None	CCT 5.5, AOC < ACC	Same	8.7
	4/23	None	—	Same	9.4
	5/22	None	—	Same	10.0
D. G. 16 mo. White	2/22	Crow +, fac. +, Trou. +, per. +	COC 3.0, AOC < ACC	None	6.3
	2/23	Same	COC 2.5, AOC < ACC	NH_4Cl, 3.5 gm. daily	—
	2/26	Crow +, fac. 0, Trou. 0, per. 0	COC 7+, ACC < AOC	Omitted	7.3
	3/ 1	Crow, Trou., fac. +	COC 3.0, AOC < ACC	None except lactic acid milk	5.4
	3/10	Crow +	COC 7+, ACC < AOC	C. L. O., 4 c.c. daily	—
	3/16	Crow +, fac. +	—	Same	5.6
	3/21	Crow +	CCT 7.5, AOC = ACC	Same	6.6
	3/26	Crow +	COC 5.0, ACC < AOC	Same plus $CaCl_2$, 3.7 gm. daily	5.6
	3/30	Crow +	COC 7+, ACC < AOC	$CaCl_2$ omitted	6.2
	5/15	Crow +, fac. 0	COC 7+, AOC < ACC	C. L. O., 4 c.c. daily	8.4

The five latent cases (Table 2) showed the same steady improvement in symptoms and the same tendency toward an increase in the concentration of the serum calcium. The rate of this increase was somewhat slower than in the active cases. The total duration of exposure required to produce an average rise of 1 mg. of calcium in 100 c.c. of serum varied from twenty-seven to one hundred minutes, and averaged sixty minutes. The average number of days of treatment was sixteen. Because of a distinct erythema which developed in S. R., exposures had to be omitted for several days and the stay in the hospital was prolonged. U. W., a colored baby, showed the slowest rise in calcium concentration.

A. C. (Table 3) showed a gradual rise in calcium from 7.1 mg. to 10.0 mg. in 100 c.c. of serum during the course of two and three-fourths

months. The diet was lactic acid milk and the treatment was 60 minims (4 c.c.) of cod liver oil daily during this period. The data also show the rapid clinical improvement resulting from the administration of hydrochloric acid in the milk (2-24, Table 3). D. G. showed a rapid initial improvement in clinical symptoms following the ingestion of ammonium chlorid, but he failed to maintain this condition when administration of the salt was stopped. During the two and one half months in which he received 60 minims (4 c.c.) of cod liver oil daily, the calcium advanced from 5.4 mg. to 8.4 mg. in 100 c.c. of serum. During five days of this time, he received 55 grains (3.7 gm.) of calcium chlorid daily, with a resulting increase in serum calcium of only 0.6 mg. in 100 c.c. It is interesting to note that the early part of the treatment of these two cases preceded the investigation of the effect of ultraviolet rays on tetany, so the two groups were under different climatic conditions. D. G., however, still had a low serum calcium

TABLE 4.—*Cases wtih Low Serum Calcium Accompanying Rickets, Treated with Cod Liver Oil*

Patient, Age and Color	Date, 1923	Symptoms of Tetany	Electrical Reaction, Milliamperes	Medication	Ca, Mg. in 100 C.c.
A. V.	5/ 4	None	—	C. L. O., 1 c.c. daily	7.6
12 mo.	5/11	None	COC 7+, AOC < ACC	Same	—
White	5/15	None	—	C. L. O., 8 c.c. daily	—
	5/18	None	COC 7+, AOC < ACC	Same	7.9
J. H., 8 mo.	5/ 4	None	COC 7+, AOC = ACC	C. L. O., 4 c.c. daily	8.4
White	5/18	None	COC 7+, ACC < AOC	Same	8.4

figure, a crow and a reversal of the anodal reaction, May 15, which was at practically the end of the period of observation on the artificial heliotherapy cases.

J. H. and A. V. (Table 4) had cases of rickets accompanied by a moderate lowering of the serum calcium concentration and changes in the anodal electrical reactions. They were selected to serve as controls because the lack of severe symptoms of tetany made active treatment unnecessary, and because they were under the same ward conditions at the same time as the patients receiving ultraviolet irradiations. Both of these patients failed to show a very appreciable rise of serum calcium in a period of time comparable to that required for the cure of infantile tetany by the use of artificial heliotherapy. Although Park [8] has proved that the effect of cod liver oil and sunlight on rickets is the same and interchangeable, the cure of infantile tetany by cod liver oil in the cases studied was much slower than with the ultraviolet rays. It is realized, however, that the small number of cases and the use of rather small doses of a cod liver oil with unknown vitamin content preclude the formation of any definite conclusions.

SUMMARY

Because infantile tetany is only temporarily improved by the use of hydrochloric acid producing substances (calcium chlorid, ammonium chlorid and hydrochloric acid), an investigation of two agents which might be expected to give more permanent relief was undertaken. The exacting standard of a return of the serum calcium concentration to 9.5 or 10.0 mg. in 100 c.c. was used to judge the completeness of the cure. Cod liver oil caused a gradual increase in the calcium of the serum over a period of several weeks. In eleven patients with infantile tetany, ultraviolet rays applied in amounts approaching the limit of tolerance, and unaccompanied by other treatment, caused a progressive and permanent relief of the clinical symptoms, paralleled by the return of the serum calcium concentration to an essentially normal figure. With the mercury vapor lamp at a distance of 50 cm., the average total exposure necessary to cause an increase of serum calcium of 1.0 mg. in 100 c.c. was fifty minutes. An average of fourteen days was required for the calcium to rise from its initial low figure to about 9.5 mg. in 100 c.c. of serum. This rise was proportionally more rapid in the cases having the lowest initial concentration of calcium.